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GASTROJEJUNOCOLIC FISTULA*

Review of Nine Cases, with Use of Vagus Resection as Part of the Operative Procedure in One

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BOSTON AND FRAMINGHAM, MASSACHUSETTS

GASTROJEJUNOCOLIC fistula following gastrojejunostomy has long been considered one of the most serious complications of gastric surgery. Historically, the initial reports on the evolution and correction of the condition include the description by Wolfer of the first gastroenterostomy in 1881, the recognition by Braun of a gastrojejunal ulcer eight years later, the finding by Czerney[1] of a fistula into the colon at the site of a previous gastroenterostomy in 1903, and the surgical intervention for the correction of the condition by de Herezel[2] in 1905.

The surgical problem is solved by removal of the fistula, restoration of bowel continuity and correction of the ulcer diathesis. Because vagus resection has not been reported as the method of dealing with this last factor, a case from the Cushing Veterans Administration Hospital is cited in which it was successfully employed after restoration of the continuity of the intestinal tract, and the data on 8 other cases of gastrojejunocolic fistula from the Massachusetts General Hospital are added.

INCIDENCE

In 1941 Bornstein[3] reviewed the literature and found only 322 cases of gastrojejunocolic fistula, thus suggesting that the experience of any one surgeon in treating the condition must, of necessity, be limited. In the past forty years there have been but 18 such patients admitted to the Massachusetts General Hospital,[4, 5] and no case has been encountered since 1941. The decreasing incidence can be explained chiefly by the steadily growing enthusiasm for gastric resection rather than gastroenterostomy in the treatment of duodenal ulcer. The extent to which this shift in the surgical approach has taken place is illustrated by a threefold increase in resections for duodenal ulcer at the Massachusetts General Hospital during recent years, as contrasted with the near disappearance of the operation of gastrojejunostomy alone (Fig. 1). Vagus resection has also been adopted during the last four years as another method of surgical treatment of an appreciable number of patients.

It is far from true, however, that gastrojejunocolic fistula can now be considered an obsolete entity. Because of the long interval between gastroenterostomy for ulcer and the occurrence of fistula (Table 1) there is bound to be a continuing residue of such fistulas for an appreciable period. Furthermore, some surgeons still perform gastroenterostomies without resection for duodenal ulcer, thus establishing the potential origin of a gastrojejunocolic fistula. In addition, partial gastric resections that inadequately control the ulcer diathesis may produce marginal ulcers, which subsequently involve the colon. Finally, during what must be considered the experimental phase in the era of evaluation of vagus resection with associated gastroenterostomy, as advocated by Dragstedt et al.[6] in the treatment of duodenal ulcer, there will be a certain number of cases in which the resection of the vagi will not be permanently effective in altering gastric acidity because of either an inadequate original operation or a possible subsequent regeneration of nerve fibers. Such patients will then present essentially the same anatomic background for fistula formation as those of the earlier period, on whom gastroenterostomy alone was carried out.

ETIOLOGY

Gastrojejunal ulcer is the inevitable precursor of a gastrojejunocolic fistula, but the exact cause of such an ulceration remains as much a matter of debate as the etiology of the duodenal or gastric

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ulcer that preceded it. It seems probable that anastomotic ulcers occur when enterostomy or gastric resection fails to control adequately the gastric hyperacidity in a patient with an ulcer diathesis.[7] The lesions represent the effect in such persons of the unneutralized acid gastric contents on the first part of the small intestine with which they come in contact. Operations for gastric ulcers

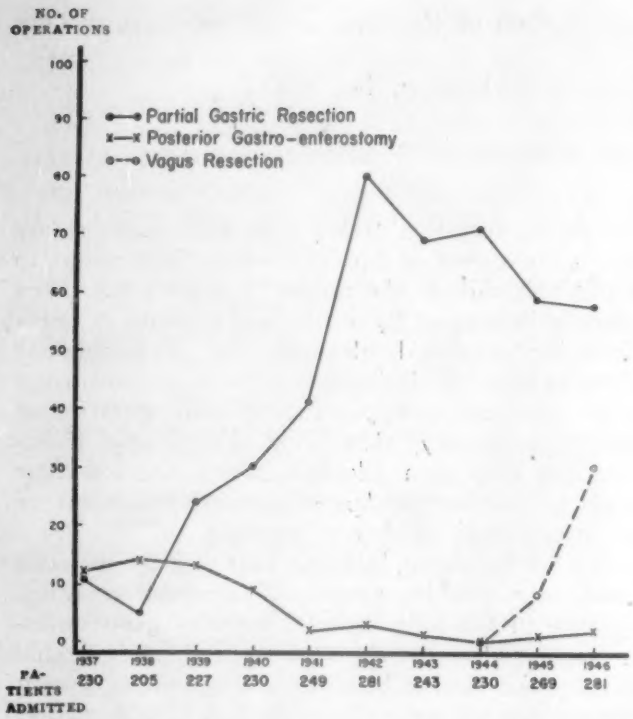

FIGURE 1. *Types of Operation for Duodenal Ulcer at the Massachusetts General Hospital, 1937-1946, Showing the Increase in Gastric and Vagus Resections and the Decrease in Gastroenterostomy as the Surgical Treatment of Duodenal Ulcer.*

A total of twenty-four other types of gastric operations, including plastic procedures and explorations, were done during this period.

are seldom attended by this complication, in contradistinction to those for duodenal ulcers.[3]

The incidence of gastrojejunal ulcers after gastroenterostomy alone varies according to different authors[8-10] from Verbrugge's[8] figure of 1.41 per cent to Hurst and Stewart's[10] 51 per cent. Balfour and Down[11] report a rate of 3.26 per cent of 500 cases, and Benedict[5] cites a comparable figure from the Massachusetts General Hospital of 2.9 per cent.

After gastric resection for benign lesions, the incidence of gastrojejunal ulcers is at the lower rate of 0.4 to 10 per cent,[12-15] and marginal ulcers are essentially never encountered in resections for gastric carcinoma, in which condition hypochlorhydria is the rule. Between 8.7 and 23.8 per cent[7, 16-22] of all marginal ulcers perforate into the transverse colon, causing gastrojejunocolic fistulas.

The time between the original operation for ulcer and the development of a fistula varies from six weeks to forty years,[3, 23] with an average of approximately seven years.[3, 16, 24] The 9 patients in the present series averaged eleven years (Table 1).

Inasmuch as duodenal ulcers are approximately four times as common in male as in female patients,[25] it is not surprising that marginal ulcers, which represent a secondary surgical complication to the condition, are relatively rare in women and that gastrojejunocolic fistulas as a further sequela are almost never encountered.

At the time the diagnosis of gastrojejunocolic fistula was made the average age of our 9 patients was forty-four years, which closely parallels the average reported in larger series of cases,[8, 26] and the individual variation of thirty-one to fifty-eight years in our cases likewise approaches the span of twenty to seventy-two years found in the literature.[8, 24]

In the period covered by this paper (1937-1947, inclusive) 5 patients were admitted to the Massachusetts General Hospital in whom gastrocolic fistulas were due to carcinoma, 1 originating in the stomach and the other 4 in the colon. These

TABLE 1. *Duration of Symptoms in Relation to Operation.*

CASE NO.	AGE AT ONSET OF FISTULA SYMPTOMS*	SYMPTOM-FREE PERIOD FOLLOWING GASTRO-ENTEROSTOMY	PERIOD BETWEEN GASTRO-ENTEROSTOMY AND DEVELOPMENT OF FISTULA	DURATION OF FISTULA SYMPTOMS BEFORE OPERATION
	yr.	yr.	yr.	
1	30	None	5	4 yr.
2	49	13	15	2 yr.
3	49	6	15	1 mo.
4	31	3	6	1⅓ yr.
5	56	6	6	2½ yr.
6	50	11	11	8 mo.
7	39	None	1	2 mo.
8	58	30	30	5 mo.
9	46	9	10	6 mo.
Average	45	9	11	1 yr., 3½ mo.

*All patients were men.

fistulas as well as those secondary to tuberculosis and other special diseases of the stomach or colon[7, 16, 22, 27] are caused by simple direct extension of the pathologic process rather than by any alteration in gastric physiology and are, therefore, not included in the present discussion.

PATHOLOGY

Depending on the site and extent of the anastomotic ulcer, the fistula may be gastrocolic, jejunocolic or gastrojejunocolic. Such fistulas are nearly always single,[3, 7] although in 1 case there were two, with a jejunal ulcer in addition. The fistulas vary in diameter from a few millimeters to 6 cm.[24] and are lined with a smooth mucous membrane, which usually shows no ulceration[3] and in which the glands are regularly disposed. The colon is often constricted at the lesion, with resulting

partial obstruction and dilatation proximal to the fistula.

An interesting feature of the lesion is that, as a rule, unless the fistula is very large the folds of jejunal mucosa act as a valve that prevents passage of gastric contents into the colon via the fistula[3, 24] (Fig. 2) but permits the regurgitation of feces and flatus into the jejunum and thence into the stomach. This explains the greater efficacy of barium enemas as compared to barium by mouth for visualizing these fistulas and further suggests why medications are ineffective in combating the diarrhea,

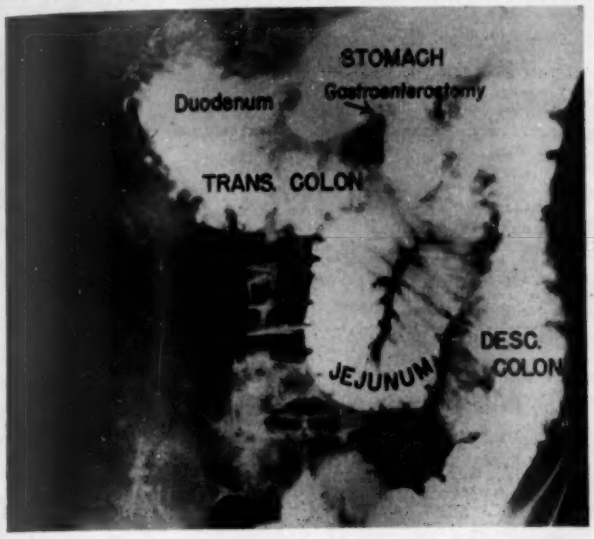

FIGURE 2. *Roentgenogram Demonstrating Stomach Filled with Opaque Material after a Barium Enema.*
No barium passed through the fistula in the reverse direction after gastric studies.

whereas a constipating diet is sometimes successful. The mechanism of the diarrhea, with its resulting loss of weight, vitamin deficiency and hypoproteinemia, therefore, is probably irritation of the small intestine by feces and not, as is commonly believed, the direct and rapid passage of gastric contents into the colon.

CLINICAL DATA

All patients were men whose original lesion was a duodenal ulcer. They were first operated on at an average age of thirty-four, approximately five years after their first symptoms; 6 posterior gastroenterostomies, 1 pylorectomy, 1 exclusion operation and 1 Billroth II were the original procedures. An average of nine years supervened before ulcer symptoms recurred, and on the average two years were added before symptoms of a fistula became evident. Even then the symptoms were allowed to persist for approximately a year before operation was carried out, so that these patients, whose ulcer symptoms usually started in their late twenties, were over forty-five years of age before they were operated on for the fistulas (Table 1).

Weight loss is the most consistent symptom in gastrojejunocolic fistulas (Table 2), being marked and rapid in over 90 per cent of the cases in spite of the fact that anorexia is uncommon. Except in patients with fecal vomiting,[24] unimpaired or even increased food intake is the rule.[3] Thus, although the appetite in 3 cases was better than usual, and decreased in but 1, 8 patients were strikingly below their normal weight. This weight loss is primarily the result of the watery or semisolid diarrhea found in two thirds of this series, but usually encountered in an even higher proportion.[16] The stools are acid and foul, owing to fatty acids, and, on occasion (as illustrated in 1 of our cases), show recognizable undigested food within an hour of its ingestion. Further manifestations of the diarrhea in two thirds of the cases are weakness, dehydration and emaciation.[3, 16] Lowered serum protein values in over 80 per cent of the cases are reported by Atwater, Butt and Priestly.[16]

TABLE 2. *Symptoms in Order of Frequency.*

SYMPTOM	NO. OF PATIENTS
Weight loss	8
Diarrhea	6
Weakness or fatigue	6
Nausea (4 cases) or vomiting (4 cases)	5
Altered appetite	4
Hematemesis (3 cases) or melena (2 cases)	3
Foul breath	3
Abdominal pain	3

About half the patients complained of fecal-smelling eructation,[16, 26] which was a more common finding than foul vomiting, since the passage of gas into the stomach from the colon takes place more readily than intestinal material and does not depend to the same degree on the fluidity of the large-bowel contents.[3] Nausea and vomiting were present in 5 cases but both were not always present in the same patient. In the absence of intestinal obstruction, vomitus that is fecal in character is pathognomonic of a gastrocolic fistula.

Hematemesis occurred in 3 patients, 2 of whom also showed melena. A somewhat lower incidence was reported by Gray and Sharpe,[26] who found gastrointestinal hemorrhage in 30 per cent of gastrojejunal ulcers before a fistula had formed and 10 per cent after the fistula had become evident. Such bleeding is the chief cause of the varying degree of anemia found in over 50 per cent of the cases,[16] although the generally debilitated state of the patients and their markedly altered nutrition undoubtedly also contribute to this finding. Gastric acidity studies are variable and of little diagnostic help, since bile and proximal jejunal contents inter-

mittently passing into the stomach neutralize the acidity to an unpredictable degree.

Abdominal pain is an undependable symptom and is less related to meals, or relief by food and alkali, than the original ulcer discomfort is.[19] Eusterman[28] states that in 85 per cent of the cases the pain is referred lower and farther to the left than that typically found with duodenal ulcer. Crampy lower abdominal discomfort accompanies partial large-bowel obstruction or irritation at the site of the lesion, whereas cessation of such pain and the onset of diarrhea suggest relief by the establishment of the fistula. There is little correlation between the location of pain and the finding of tenderness, and, in fact, the physical examination rarely reveals any significant findings except for abdominal scars and evidence of emaciation. Occasionally an inflammatory mass can be felt,[3, 7, 26] as in 2 of our cases.

Roentgenologic study of the intestinal tract by barium enema is the most helpful diagnostic procedure. Because of the valve-like action of the jejunal mucosa described above, a barium enema is more likely to demonstrate the fistula than a gastrointestinal series. This fact was emphasized in the report by Gray and Sharpe[26] of 49 cases confirmed by operation in which the fistula was revealed in only 13 of the 40 patients who had stomach x-ray films taken, whereas it was shown in all of the 25 studied by barium enema. In the present series, barium enema revealed the lesion in 5 of the 6 cases in which this procedure was carried out, whereas 4 of the 7 gastrointestinal series failed to reveal the fistula.

Enemas to which distinctive coloring matter has been added reveal the condition if the dye can be recovered by gastric lavage, and similar coloring material taken by mouth and found in the stool within a short period is suggestive of the diagnosis.

Treatment

There is no satisfactory medical treatment for gastrojejunocolic fistulas. Few diseases present a greater challenge to the proper timing and selection of surgical intervention without which the prognosis in this condition is progressive inanition and an early death from perforation, hemorrhage or intercurrent disease.[3, 8, 29, 30]

The first objective of treatment is to restore the patient to sufficiently good condition to withstand the formidable operative attack upon the fistula itself. This may be accomplished by medical measures alone if the condition has not persisted so long that emaciation is marked. The importance of intelligent use of blood transfusions, parenteral fluids and chemotherapeutic agents, both as a preliminary and as an adjunct to surgery, cannot be overstressed, and undoubtedly such measures are of prime significance in the marked lowering of the mortality rate in recent years. In certain cases, however, the effects of a long period of depletion may be so pronounced that supportive measures alone will be unavailing as adequate preoperative preparation unless the vicious circle of the self-perpetuating diarrhea is interrupted. Pfeiffer[30] was the first to emphasize the efficacy of a proximal shunt of the fecal stream to accomplish this end, and his advocacy in 1939 of an ascending colostomy as a preliminary procedure to corrective surgery stands as the most important single contribution to the treatment of gastrojejunocolic fistulas. With its adoption, the mortality has been reduced from levels as high as 63 per cent[31] to below 5 per cent,[22] and although many other types of side-tracking operations have been advanced by Marshall,[21] Dreosti,[17] Lahey[19] and others, none have proved superior to the originally advocated ascending colostomy in simply achieved effectiveness. Before the period of chemotherapy, peritonitis in these debilitated patients often followed even the simple procedure of colostomy or cecostomy, and 2 of the patients in this series on whom these procedures were carried out died in eight and fourteen days of peritonitis (Table 3).

After the initial treatment by appropriate medical or surgical measures, the problem of interrupting the fistulous tract must be met. This has been accomplished by many surgical procedures, including

Table 3. *Results of Operation.**

Case No.	Date†	Original Operation	Preliminary Operation for Fistula	Fistula Operation First Stage	Final Definitive Operation	Outcome
1	1937	Posterior gastroenterostomy	Jejunostomy	—	Gastric resection‡	Relief
2	1938	Posterior gastroenterostomy	—	Excision and restoration	—	Death
3	1938	Exclusion operation	—	—	Gastric resection‡	Relief
4	1939	Billroth II procedure	Colostomy	—	—	Death
5	1939	Posterior gastroenterostomy	—	Excision and restoration	Gastric resection	Death
6	1940	Posterior gastroenterostomy	Cecostomy	—	—	Death
7	1941	Posterior gastroenterostomy	—	Excision and restoration	Gastric resection	Relief
8	1941	Pylorectomy	—	—	Gastric resection‡	Relief
9	1947	Posterior gastroenterostomy	—	Excision and restoration	Transthoracic vagotomy	Relief

*A duodenal ulcer was the original lesion in all the cases.

†Date of operation for fistula.

‡Excision of the fistula was of necessity part of the operation.

simple division and closure of small fistulas, excision of the fistula and gastroenterostomy stoma with substitution of other varying types of gastroenterostomies with and without gastric resection, and *en-bloc* removal of the area of stomach, jejunum and colon involved in the fistulous process with re-establishment of the normal continuity of the intestinal tract. Progress and changes in the field of medicine, including the advent of chemotherapy, have led to certain modifications in the surgery of this condition but have not lessened the technical difficulties invariably presented by an inflammatory mass involving the upper and lower intestinal tract in a region distorted by the adhesions and altered anatomy resulting from the earlier operation.

Of the 7 patients in our series in whom a direct attack was made upon the fistula (1 of whom died of bronchopneumonia four days postoperatively), 4 had a resection of the fistula with restoration of intestinal continuity. In the remaining 3 gastric resection was carried out at the same time the fistula was surgically corrected. Although these patients all survived, there is a very considerable added hazard in this procedure.[3, 24, 33]

The final phase in the treatment, unless a definitive surgical procedure has already been carried out, lies in dealing surgically with the patient's ulcer tendency, which has so insistently asserted itself by multiple manifestations in the past. With the patient's almost immediate improvement after correction of the fistula, the surgeon is often tempted to postpone further operation indefinitely. Such an attitude shows an understandable but misdirected consideration for the patient, for many reports[4, 34] bear out the finding that if the intestinal continuity is restored a duodenal ulcer will again develop in from 20[34] to 40 per cent[19] of the cases. This proneness to recurrence is well illustrated by the fact that in this series all 3 of the surviving patients in whom the normal anatomy of the intestinal tract was re-established exhibited new duodenal ulcers within three months to a year. All these patients were again operated upon after the recurrence of symptoms, and 1 of them died from peritonitis five days after a gastric exclusion operation.

Selection of a simple gastroenterostomy as the final definitive operation would merely serve to invite a repetition of the unfortunate train of events and would, in addition, show a disregard of the growing tendency to abandon such an operation for the treatment of this condition as pointed out above (Fig. 1).

Gastric resection by one of the accepted technics has generally been used as the procedure of choice but is uniquely difficult and hazardous to perform because of adhesions and distortion due to the multiple antecedent operations in these patients. It was to avoid these technical intra-abdominal difficulties that consideration was given to transthoracic vagotomy as the definitive operation to correct the ulcer diathesis in patients without pyloric obstruction.

In the following case this plan of treatment was successfully carried out. So far as we can determine this is the first report of a case in which such an operative policy was adopted, although before the definitive operation cited, the potential role of vagotomy in the treatment of gastrojejunal fistula was also suggested by Barber.[32]

Case Report

J. C. S. (C. V. A. H. 1149), a 46-year-old single box maker, was well until the age of 34 years, when he underwent operation for a perforated peptic ulcer. Two years later posterior gastroenterostomy was done. He was then asymptomatic for 9 years, when pain recurred, this time in the left upper quadrant. Nine months later at the age of 46 he developed weakness, faintness and sweating, followed in 1 week by approximately nine bowel movements every night. His

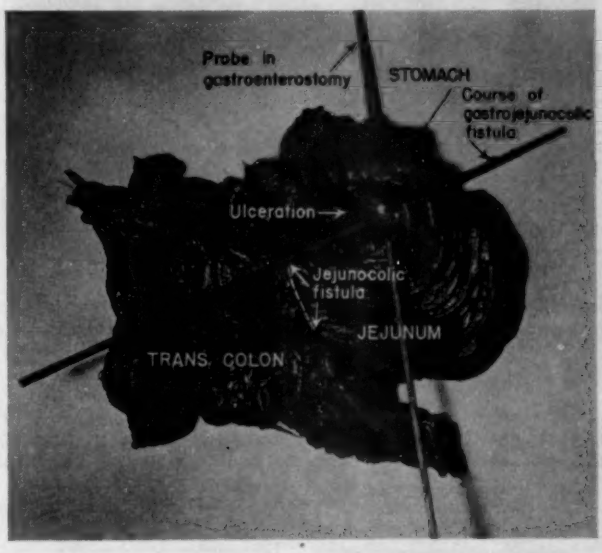

Figure 3. *Specimen Showing a Fistula 2.5 cm. in Diameter Opposite the Gastrojejunal Stoma.*

The resected portion of stomach is largely obscured by the opened jejunum.

nocturnal diarrhea continued for 5 months, during which he lost 20 lb. before his first admission to the Cushing Veterans Administration Hospital on December 16, 1946.

Physical examination revealed pallor, moderate emaciation and clubbing of the fingernails. The abdomen was protuberant, and an indefinite upper abdominal mass was palpable. Laboratory examinations were negative, except for a hemoglobin of 12.2 gm., a white-cell count of 14,050 and a total protein of 6.3 gm. per 100 cc. Charcoal administered by mouth was passed by rectum in 2 hours and 10 minutes. A barium enema revealed a gastrojejunocolic fistula (Fig. 2), although upper gastrointestinal x-ray studies characteristically failed to reveal the lesion.

Preoperatively, the patient was given 2 gm. of sulfathaladine four times a day, and a total of 300,000 units of penicillin intramuscularly. The posterior gastroenterostomy and fistula were excised *en masse* (Fig. 3), including a segment of the greater curvature of the stomach. The stomach was closed, and the continuity of the jejunum and of the colon was re-established by means of end-to-end anastomoses. The gastrojejunocolic fistula was 2.5 cm. in diameter and opposite the gastrojejunal stoma, which was of similar size.

The postoperative course was uneventful. X-ray examination of the upper gastrointestinal tract 1 month after a leave from the hospital showed no evidence of ulcer. The fasting

FIGURE 4. *Duodenal Ulcer Developing Three Months after Restoration of Intestinal Continuity Following Excision of a Gastrojejunocolic Fistula.*

gastric content contained no free hydrochloric acid and 10° of total acidity. He was discharged and readmitted 1 month later because of a 2-week history of right-upper-quadrant

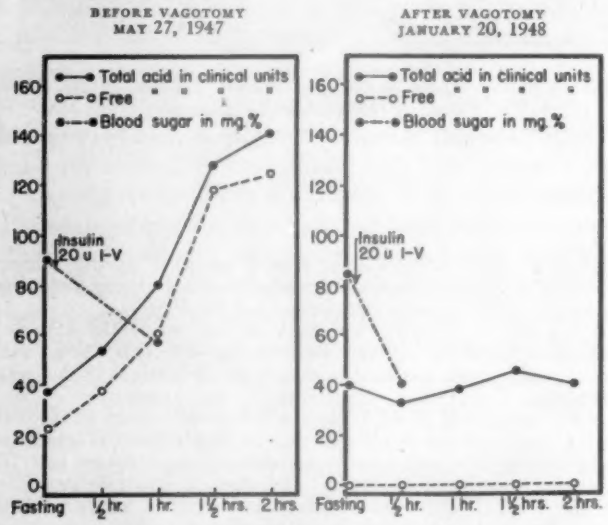

FIGURE 5. *Insulin Tests before and after Vagotomy, Showing the Absence of Increased Acidity that Followed Insulin Hypoglycemia as an Indication of the Effectiveness of Vagus Resection.*

pain. He now had tenderness over the right upper quadrant and the fasting gastric content contained 51° of free hydrochloric acid and a total acidity of 75°. X-ray examination showed an ulcer crater, 1 by 2 cm., in the duodenal cap (Fig. 4). A transthoracic vagus resection was done.

On the 18th postoperative day the patient had hematemesis, followed by melena. He continued to bleed for 5 days, during which he received 5½ pints of blood. Two months later there was no x-ray evidence of ulcer, and the insulin test (Fig. 5) was consistent with complete vagus resection. One and a half years after the excision of the fistula and one year after the vagus resection he was asymptomatic and had well healed abdominal and thoracic scars. No free acid was secreted after insulin hypoglycemia. X-ray examination revealed no evidence of ulcer. The patient had gained back his 20 pounds in weight.

DISCUSSION

The case reported above re-emphasizes a number of fundamental considerations and introduces certain factors for further speculation. In the first place, the initial satisfactory response following extirpation of the fistula without a preliminary colostomy bears out the fact that, if the patient's condition is satisfactory, a first-stage operation with its inevitable soiling of the abdominal wall and need of eventual closure may be unnecessary. In case of doubt, however, such a procedure should be performed, but even this may be unavailing in avoiding a fatal outcome, as illustrated by Cases 4 and 6 in our series, if the patient's general condition is below a critical level.

A second fact illustrated by the case cited is that, if intestinal continuity is restored, the patient may develop an ulcer even though his progress is being followed by frequent visits, and thus he may be a less favorable candidate for a definitive surgical procedure than he would have been had such a final step been taken before discharge from the hospital.

Another interesting fact is the massive intestinal hemorrhage, presumably from the reactivated duodenal lesion that occurred eighteen days after vagotomy. After such an interval, it would be expected that, if the operation had been effective, healing of the ulcer would have progressed to a stage at which bleeding could not well have occurred. There can be little doubt from the findings of the insulin test, as well as the fact that both vagi were resected from 8 cm. above the diaphragm to below the point at which they arborize, that the procedure had interrupted all impulses that might have reached the stomach over these nerves.

The possibility of performing vagotomy by the subdiaphragmatic route at the time the fistula is excised is naturally one that must be considered. The fact that it spares the patient further surgical treatment is an obvious advantage but one that seems to be more than outweighed by the possible contamination of the vulnerable subdiaphragmatic area by the potential soiling attendant on carrying out the anastomosis of the transverse colon. It is important to remember that with excision of the fistula and restoration of the intestinal tract there is bound to be a brief respite from ulcer symptoms during which the patient's general condition can

still further improve before he is again subjected to the added risk of a definitive surgical operation. Furthermore, there are apt to be technical difficulties in satisfactorily exposing the esophageal hiatus by the subdiaphragmatic route because of adhesions from the previous operation and existing inflammatory reaction. These difficulties are obviated by a transthoracic approach to the final operation, and in such cases vagotomy can probably be carried out most effectively by such a route.[35]

Summary and Conclusions

The findings in 9 cases of gastrojejunocolic fistula are presented, and the literature on the subject is reviewed.

The symptomatology is usually attributable to the secondary effects of diarrhea induced by the reflux of irritating large-bowel contents into the upper jejunum and stomach. Passage of gastric material into the colon through the fistula in the reverse direction is delayed, as a rule, by a valve-like action of the jejunal mucosa.

The treatment of gastrojejunocolic fistulas is surgical and consists of removing the fistula, restoring bowel continuity and correcting the ulcer diathesis.

Preparation of the patient for excision of the fistula should include the institution of an ascending colostomy as recommended by Pfeiffer as a preliminary procedure in all patients whose general condition is unsatisfactory.

The tendency in these patients to reactivate an ulcer after an excision of the fistula and restoration of intestinal continuity is so strong that unless corrective surgical measures have been carried out at the earlier operation they should be adopted before the patient is finally discharged from the hospital.

A case is cited for the first time in which, after excision of the fistula, transthoracic vagotomy was used as the definitive treatment of the ulcer diathesis. This patient was asymptomatic a year after the vagus resection.

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HEPATITIS WITHOUT JAUNDICE AND WITHOUT HEPATOMEGALY

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MALDEN, MASSACHUSETTS

FOUR cases of hepatitis without jaundice and without hepatomegaly constitute the material of this report. Hepatitis without jaundice has been variously described as a "mild disease"[1] and "mild non-icteric form of hepatitis,"[2] running a course of six to eight weeks. A review of the literature reveals that an enlarged and tender liver is an essential finding in virus hepatitis and in the hepatitis seen in infectious mononucleosis. The cases presented below were severe illnesses running a four to six months' course. The liver was not enlarged, but instead a sharply circumscribed area of localized tenderness in the right upper quadrant was elicited in all cases. The protracted course, marked by exacerbations and remissions, was associated with marked psychologic turmoil. Whether this fact was an integral part of the disease or a consequence of chronic illness remains open to question. At any rate, irrespective of source, the management of this aspect of the illness proved to be most difficult and is worthy of emphasis.

Case Reports

Case 1. D. G., a 20-year-old student nurse, was first admitted to the hospital on November 10, 1947, complaining of aching pain in the right upper abdomen, nausea at sight of food, loss of appetite and vomiting of 4 days' duration. She was seen, as an outpatient, at the onset of illness, on the Surgical Service and after twenty-four hours it was decided that surgical treatment was not indicated. The white-cell count at that time was 13,400, with 82 per cent neutrophils.

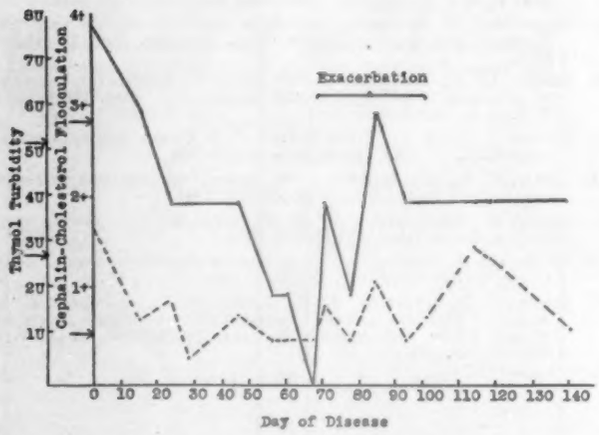

Figure 1. *Relation of Liver Function to Clinical Course in Case 1.*

The patient had not received plasma, blood or inoculations within the 6 months prior to admission. There was no known exposure to chemicals or to patients with virus hepatitis.

The family and past histories and a system review were all noncontributory to the present illness.

Physical examination revealed a well developed, well nourished patient who was not acutely ill. Complete examination revealed normal findings except for a sharply circumscribed area of localized tenderness without spasm in the right upper quadrant just lateral to the midline. This was associated with tenderness to jarring over the right lower thoracic cage. The liver and spleen were not palpable, and there was no lymphadenopathy.

The temperature was 99°F., the pulse 80, and the blood pressure 126/84.

On November 11 the white-cell count was 8000, with 58 per cent neutrophils and 40 per cent lymphocytes. The erythrocyte sedimentation rate was 14 mm. per hour. The urine was negative for bile, and urobilinogen was present in a dilution of 1:16 (normal 1:8). The icteric index was 5 units; the prothrombin time was 68 per cent of normal. The initial cephalin-cholesterol flocculation was +++, and the thymol turbidity was 3.5 units (normal 2 units).[3] The prothrombin time, after 1 week, was 82 per cent of normal and remained above this value for the duration of the hospital stay. Urinary urobilinogen varied from 1:4 to 1:16, and the white-cell count from 6000 to 8000, with 35-40 per cent lymphocytes. The heterophil-antibody agglutination and gall-bladder and gastrointestinal series were negative. Erythrocyte sedimentation remained within normal limits. Repeat cephalin-cholesterol flocculation and the thymol turbidity tests during both periods of hospitalization are shown in Figure 1.

Glucose (5 per cent) in physiologic saline solution and protein hydrolysate were given intravenously in the first 60 to 72 hours because of almost complete anorexia and vomiting. Subsequent treatment consisted of absolute bed rest, a diet consisting of 250 gm. of carbohydrate, 100 gm. of protein and 80 gm. of fat, multi-vitamins, components of the vitamin B complex and vitamin K in therapeutic doses daily and supplementary high-protein drinks. At first methionine and choline (1 gm. each, three times daily) were given, but they were discontinued within 3 to 4 weeks, partly because of inability to disguise the amino acid in a palatable drink.

The appetite remained poor, and there was a 15-lb. weight loss in 1 month. The clinical course was characterized by exacerbations manifested by anorexia, nausea, general malaise and increased tenderness in the right upper quadrant. In some instances this was reflected by a rise in the cephalin-cholesterol flocculation and thymol turbidity tests. After 6 weeks it seemed that the patient had reached a *status quo* and she was discharged on December 24 to the care of her family, who had received careful and detailed instructions regarding convalescence.

The patient was readmitted on December 30 complaining of severe anorexia, continuing weight loss, overwhelming and seemingly progressive fatigue and varying right-upper-quadrant distress.

Physical examination revealed evidence of further weight loss to 110 lb., and the positive findings consisted of tenderness to palpation in the right upper quadrant in exactly the same area described in the previous physical examination. This was again associated with tenderness to jarring over the right lower thoracic cage.

The cephalin-cholesterol flocculation was ++, though the thymol turbidity was within normal range, being 1.3 units. There were no other significant findings.

The therapeutic measures employed were essentially the same as those for the previous hospitalization.

The patient was again discharged on February 19, 1948, when it seemed that she had started to improve — that is, her appetite was better, the right-upper-quadrant tenderness was minimal, and there had been a slow weight gain of 2 lb. Approximately 7 to 10 days after discharge she suffered another exacerbation. She returned for a trial on duty on April 23, approximately 5½ months after the onset of the illness. However, after 1 month on duty, she suffered another

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exacerbation, and the cephalin-cholesterol flocculation was +++.

Case 2. M. G., a 20-year-old student nurse, was admitted to the hospital on November 24, 1947, complaining of vague abdominal distress consisting of "fullness" and aching in the upper abdomen associated with frequent eructation of 6 days' duration. This was followed by nausea without vomiting and anorexia so that she had eaten little or nothing for 24 to 36 hours prior to admission; moreover, the mere sight of food nauseated her. On each of three successive days, prior to admission, she had noticed "light, almost clay-colored stools" — no change in the color of the urine had been noted. In addition to these findings she had been listless and depressed.

There was no history of plasma or blood infusion or inoculations within 6 months or exposure to chemicals. She was,

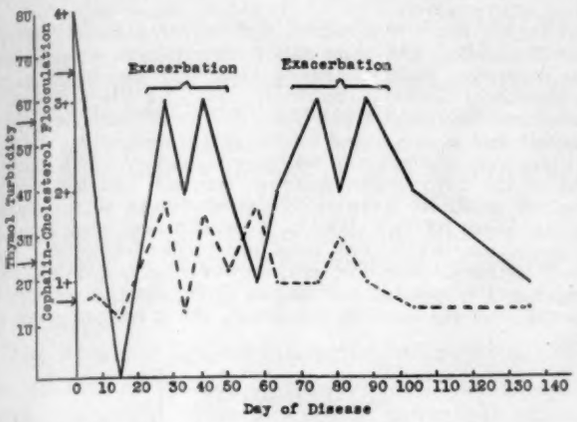

Figure 2. *Relation of Liver Function to Clinical Course in Case 2.*

however, quartered in the same building as the patient in Case 1.

The family and past histories and a system review were all noncontributory to the present illness.

Physical examination revealed a well developed, well nourished patient, who was not acutely ill. Examination showed normal findings except for tenderness without spasm in the right upper quadrant. The liver and spleen were not palpable, but there was tenderness to jarring over the right lower thoracic cage.

The temperature was 99°F., the pulse 80, and the blood pressure 110/80.

On November 24 the white-cell count was 7500, with 32 per cent neutrophils and 64 per cent lymphocytes. The erythrocyte sedimentation rate was 21 mm. per hour. The urine was negative for bile, and urobilinogen was present in a dilution of 1:8. The icteric index was 11 units. The prothrombin time was 78 per cent of normal. The cephalin-cholesterol flocculation was ++++, and the thymol turbidity was 1.6 units. The heterophil-antibody agglutination was negative, as were a gall-bladder and a gastrointestinal series. Subsequent liver-function tests are recorded in Figure 2.

The treatment was the same as that in Case 1.

Within a few days of admission the right-upper-quadrant distress became more marked and more sharply localized, and at the same time the patient complained of aching in the left upper quadrant. Examination revealed a palpable, tender spleen. There was a 6-lb. weight loss in 2 weeks. On December 8 she felt much better — that is, the right-upper-quadrant tenderness had markedly diminished, and the spleen was no longer palpable. From this time on gradual improvement was noted, and she was discharged on December 20 to the care of her parents, who had been instructed regarding convalescence.

The patient was readmitted 8 days after discharge, complaining of recurrence of fatigue, anorexia, nausea without vomiting and distress in both upper quadrants.

Physical examination was essentially the same as on the previous admission, showing tenderness without spasm to palpation in both upper quadrants associated with tenderness to jarring over the right lower and left lower thoracic cage. The temperature was 99.4°F.

The only significant laboratory findings were a cephalin-cholesterol flocculation of +++ and a thymol turbidity test of 3.7 units on the day of discharge; on the day of readmission these values were, respectively, ++ and 1.3 units. Subsequent liver-function tests are recorded in Figure 2. Cerebrospinal-fluid examination, which was done for reasons explained below, showed a protein of 45 mg. per 100 cc. but no cells.

The treatment was the same as that on the previous admission.

There were three well defined exacerbations, manifested by nausea, anorexia, general malaise, headache and increased distress in the upper quadrants, with increased tenderness to palpation. The spleen was occasionally palpable, but the liver was not felt. The exacerbations were rather accurately reflected by the liver-function tests.

On January 17, 1948, because of persistent headache, a lumbar puncture was done to rule out a complicating encephalitis and the findings were as listed above. On January 25 the patient began to feel better as manifested by amelioration of symptoms and abdominal tenderness. She was discharged but has been followed as an outpatient, and her course has been one of slow gradual improvement. She was back on duty 4½ months after the onset of illness.

Case 3. N. S., a 21-year-old student nurse, was admitted to the hospital on November 17, 1947, complaining of nausea and lack of appetite of 5 days' duration. She had not been well for 2 or 3 months before admission because of fatigue and weakness, but repeated examinations at sick call had been negative. Four or five days prior to admission, however, a

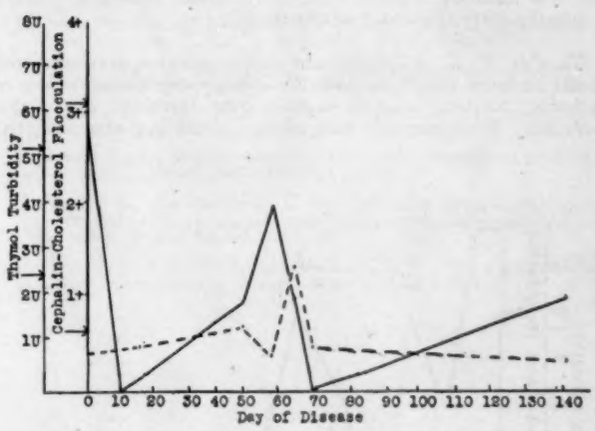

Figure 3. *Relation of Liver Function to Clinical Course in Case 3.*

decided change had occurred in the form of intense nausea without vomiting, general malaise, anorexia with an aversion to food and marked fatigue.

There was no history of plasma or blood infusion, inoculations or exposure to chemicals within the last 6 months. The patient, being a student nurse, was quartered in the same building as the patients in Cases 1 and 2.

The family and past histories and a system review were noncontributory to the present illness.

Physical examination revealed a well developed, well nourished patient, who was not acutely ill but appeared rather listless. Complete examination disclosed normal findings except for tenderness to palpation in a sharply localized area in the right upper quadrant. There was no associated muscle spasm, but there was tenderness to jarring over the right lower thoracic cage. The liver and spleen were not palpable, and there was no lymphadenopathy.

The temperature was 99.2°F., the pulse 80, and the blood pressure 110/72.

On November 18 the white-cell count was 5400, with 59 per cent neutrophils and 31 per cent lymphocytes. The sedimentation rate was 17 mm. per hour. The icteric index was 6 units. The prothrombin time was 67 per cent of normal. The urine was negative for bile, and urobilinogen was present in a dilution of 1:8. The cephalin-cholesterol flocculation was +++, and the thymol turbidity was 0.8 units. Repeat performances of these tests at regular intervals yielded normal values, and subsequent liver-function tests are recorded in Figure 3.

Except for minor variations, therapy was the same as that described for Cases 1 and 2.

This patient's illness was a comparatively mild one, though for the first 10 days, anorexia and right-upper-quadrant distress were quite marked. The discomfort gradually subsided, however, and the appetite returned slowly after a minimal loss of weight. The patient was discharged to her home for further convalescence.

She was readmitted 3 weeks after discharge, with a history of a bout of diarrhea beginning 2 days after discharge and consisting of 4 or 5 loose, nonbloody stools daily, without cramps, that lasted for 5 days. Subsequently, she became anorexic, and right-upper-quadrant distress returned.

Physical examination was negative except for a temperature of 99.2°F., and minimal tenderness to palpation in the right upper quadrant.

Laboratory findings of significance were a cephalin-cholesterol flocculation of +, a thymol turbidity of 1.4 units and a prothrombin time 66 per cent of normal. Gall-bladder and gastrointestinal series were negative. Heterophil-antibody agglutination was also negative. The prothrombin time after 10 days of vitamin K therapy was 88 per cent of normal.

The same treatment as on the previous admission was given.

Again, this patient's illness was comparatively mild, though prolonged. Her appetite gradually returned, and right-upper-quadrant tenderness remained minimal. From then on improvement was gradual and without exacerbations. She was discharged on January 27, and she returned to duty 4 months after the onset of the illness.

Case 4. R. K., a 29-year-old graduate nurse, was admitted to the hospital on November 26, 1947, complaining of loss of appetite, nausea, general malaise and lassitude of 3 days' duration. This patient was charge nurse on the pediatric

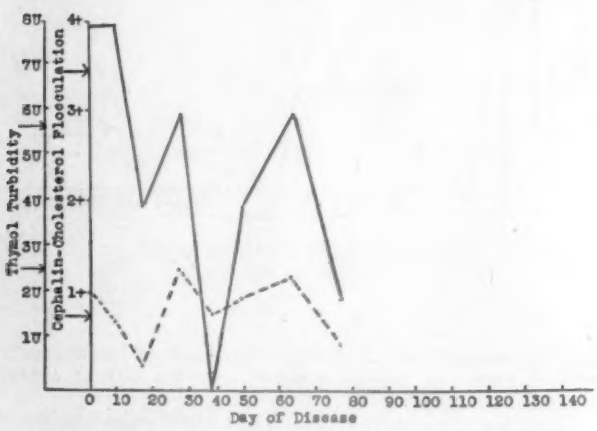

Figure 4. *Relation of Liver Function to Clinical Course in Case 4.*

floor where 2 of the other 3 patients had worked, and she had been active in the care of these patients.

There was no history of plasma or blood infusion, inoculations or exposure to chemicals within the last 6 months.

The family and past histories and a system review were noncontributory to the present illness.

Physical examination revealed a well developed, well nourished woman who was not acutely ill. Complete examination disclosed normal findings except for a definite, sharply localized area of tenderness in the right upper quadrant associated with tenderness to jarring over the right lower thoracic cage. The liver and spleen were not palpable, and there was no lymphadenopathy.

The temperature was 99.6°F., the pulse 74, and the blood pressure 100/60.

On November 26 the white-cell count was 6500, with 63 per cent neutrophils and 32 per cent lymphocytes. The sedimentation rate was 21 mm. per hour. The icteric index was 5 units; the prothrombin time was 80 per cent of normal. The urine was negative for bile, and urobilinogen was present in a dilution of 1:4 to 1:8. Cephalin-cholesterol flocculation was ++++, and the thymol turbidity was 2.1 units. Periodic performance of the above tests were all normal, and subsequent liver-function tests are recorded in Figure 4.

The treatment was the same as that for the 3 previous cases.

Clinically, there was marked anorexia, nausea, right-upper-quadrant tenderness and a 12-lb. weight loss in 2 weeks. After approximately 3 weeks the patient began to improve — that is, the appetite returned, right-upper-quadrant tenderness diminished, and there was a slow gain in weight. She was discharged to her home on December 24. Blood taken on the day of discharge, however, revealed a +++ cephalin-cholesterol flocculation and 2.6-unit thymol turbidity. She was followed at home, and for the first 6 weeks there she did not fare well: the appetite was poor, nausea recurred, tenderness in the right upper quadrant returned and her weight dropped to 90 lb. (the weight at the onset of the illness having been 100 lb.). Within a week there was decided improvement, which has been progressive except for one minor setback. She has not, however, regained her lost weight and at present she weighs 92 lb. At this writing, 5 months after the onset of the illness, she is not yet ready to work.

Epidemiology

It is perhaps fair to assume that Case 1 was the source of infection for the remaining 3. The source of infection for the first case, however, was not known. The history, as elicited, rules out plasma or blood infusions, chemicals and inoculations. All 4 patients lived in the same building, and the fact that only 3, out of about 50 persons, succumbed to exposure to the first case is perhaps best explained according to Newman[4] — that is, the liver is phasic in activity, and hence susceptibility to infection is variable; thus the phase of susceptibility at time of exposure determines whether or not a person will succumb to infection.

Discussion

The presence of an enlarged liver is mentioned in all articles on hepatitis without jaundice.[1, 2, 5, 6] As mentioned above the liver was not palpable in this group of cases. There was, however, in each case a sharply localized area of tenderness in the right upper quadrant toward the midline, and this was associated with tenderness to jarring over the right lower thoracic cage. This finding, in my experience, was as significant as an enlarged liver and served as a reliable index to the clinical state.

The clinical course is marked by exacerbations and remissions characterized by varying degrees of anorexia, fluctuating intensity of right-upper-quadrant tenderness and varying degrees of generalized malaise. Some exacerbations are accompanied by a rise in temperature. Anorexia is a constant and

early symptom and may be severe enough to result in significant weight loss. Appetite and weight loss are only painstakingly regained. The long, rather than short, course makes subsequent chronic liver disease, as mentioned by Chaikin and Chlenoff,[7] an eminent possibility.

The long course of the illness was attended by marked psychologic disturbance, which, to say the least, complicates the management and treatment. The constant urging and prodding to "eat more" soon engenders in the patient an antagonism for food manifested by a mildly belligerent insistence that "I'm eating as much as I can." The weight lost was only slowly regained, if at all. With prolonged bed rest time soon weighs heavy, particularly in young vigorous adults. Attempts to counteract this by means of occupational therapy were, on the whole, only partially successful.

The cephalin-cholesterol flocculation as mentioned by others[8–11] proved to be a sensitive and reliable test and seemed to bear a relation to the clinical course. The thymol turbidity did not reach the high values reported elsewhere but did show a delayed rise occurring after clinical manifestations of activity.[12–14]

The negative heterophil-antibody agglutination, the absence of lymphadenopathy and the absence of the "atypical" lymphocyte of infectious mononucleosis seem to rule out that disease. The negative history regarding plasma or blood infusions and inoculations, for six months prior to onset of illness, eliminates homologous serum jaundice as a possibility.

Summary

Four cases of hepatitis without jaundice and without hepatomegaly are presented. The finding of a sharply circumscribed area of localized tenderness in the right upper quadrant was elicited in all cases and appeared to be as significant as a palpable liver.

The course of the disease was long and severe and resulted in the appearance of functional factors that proved difficult to manage.

The cephalin-cholesterol flocculation seemed to be the most sensitive and reliable index of both the liver function and the clinical course.

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ACUTE FOCAL EDEMA OF THE BRAIN IN CHILDREN WITH HEAD INJURIES*

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ON MARCH 18, 1943, the very active two-and-a-half-year-old son of a surgical colleague fell from his high chair with such force that his head bounced on the floor. He seemed dazed for a moment or two but had no definite period of unconsciousness. He cried loudly for a few minutes, as one might expect, but soon seemed to forget all about the fall and was apparently as well as ever. He ate his supper with a good appetite, and was put to bed. Two hours later he began to vomit; he was very pale and his skin was moist and cold, and he was very drowsy, with occasional convulsive twitchings of the right arm and leg. His mother, who is a nurse, believed that he had a severe head injury, so he was taken at once to the hospital. On arrival he was found to be in shock, with poor peripheral circulation and a low temperature; he was semicomatose and had greatly depressed reflexes and motor power of the right arm and leg, and he was admitted with the diagnosis of extradural hemorrhage as a dangerously ill patient. Treatment for traumatic shock was started, and preparations for a cranial exploration were got under way. At about the time when these were completed his condition began to improve; the signs of shock lessened, the semi-coma lightened, the reflexes on the right side became more active, and he moved his arm and leg with more power. In four hours he was so much better that it was evident that exploration would not be needed, and by the next morning, some sixteen hours after the injury, he was fully conscious and happy, with no evident neurologic abnormality. X-ray films of the skull showed no fracture. About a week later a mild bronchopneumonia, which responded well to treatment with sulfadiazine, developed. Recovery was otherwise without incident, and he was discharged at the end of three weeks. He has been examined often since then, and has at no time shown any remaining evidence of the injury.

The course of events in this case left me at a loss for an accurate explanation, when the need for proper diagnosis arose. At my first examination, the child presented an almost classic picture of a patient with compression of the brain from an extradural hemorrhage, but it did not seem reasonable to hold to this diagnosis in view of the rapid and complete clearing up of signs and symptoms without operative relief. It was evident that there had not been time for the absorption of an extradural hematoma or of a subdural collection of blood causing the same sort of local pressure. The possibility that the sudden relief of symptoms was due to the spreading into a thin layer of a previously localized blood mass in either the extradural or the subdural space was considered, but this seemed to be quite unlikely without some residual effect. Local contusion of the cortex, with its associated actual tissue damage, could have accounted for the signs of motor and reflex involvement, but here again, the recovery came too soon. An acute focal edema of the brain, bringing about the same sort of local ischemia as that caused by an extradural hematoma, could have caused the conditions present when the boy was admitted; it could have been resolved quickly enough to allow the speed of improvement shown; and it could quite properly have been expected to clear up without permanent brain damage. As there seemed to be no better explanation, this was accepted as a working diagnosis, and further examples were sought for, in the hope of proving or disproving the actual existence of such a focal edema.

This occurrence of clinical findings strongly suggesting extradural bleeding but apparently due to some other condition has been noted in the writings of others interested in this subject. The only actual case reports that I have found so far were published by Boston observers some fifty years ago. The first one, by Walton and Brooks,[1] gives the history of a young woman who was thrown from a horse, struck her head violently against a rail, and developed signs suggesting middle meningeal hemorrhage. At operation, neither extradural nor subdural bleeding was found, but on opening the dura the surgeon released about half an ounce of clear serum, and believed that the brain was edematous but otherwise normal. The patient improved slightly for a time, but then became worse and died. Post-mortem examination showed a few small areas of deep hemorrhage, none of which explained the unilateral paralysis, and the authors concluded that this had been caused by local edema. In the course of their discussion they said:

> It is not uncommon in children to find local paralysis following blows upon the head, closely simulating the results of hemorrhage, but completely disappearing in the course of a week or two, a fact which has to be borne in mind in making the diagnosis of middle meningeal hemorrhage in early life. The case here reported, together with others which have been called to our attention, would seem to indicate that similar conditions may obtain in adult life. Whether this pathology is accepted or not, the practical bearing of such cases upon our experience is to throw a certain weight in favor of conservatism in doubtful cases, though by no means lessening the demand for operation in the typical case.

The second patient, reported by Walton,[2] was a six-year-old boy who was struck by a bicycle and

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was dazed but not made unconscious. Later, he had some fever and vomited. He was fairly well until twenty-four hours later, when he became first drowsy and then unconscious, with paralysis of the right arm, leg and face. The right pupil was larger than the left, but reacted to light; there was incontinence of urine and feces, and pressure on a contusion behind the left ear caused crying. Nine hours later he was partially conscious and was regaining the use of the paralyzed muscles, so that operation was delayed. Six days after the accident he was completely well, except for a complicating sore throat, which was considered to be a coincidence. The third report, also by Walton,[2] concerned a three-and-a-half-year-old girl who was thrown to the floor from a small swing and struck her head. She was dazed, and later vomited. On the following day she had paralysis of the left arm, and exploration of the head was advised. Overcrowding of the hospital caused a delay of twelve hours, by which time she seemed much better and was beginning to use the left hand, so that no operation was done. Her convalescence was rapid, and she made a quick and complete recovery, being entirely well when seen two years later. Walton regards these patients as having had subarachnoid serous exudation and says:

> That a more or less diffuse oedema, whether involving the subarachnoid cavity or the brain itself, or both, and whether accompanied or not by marked laceration, may play a part in prolonging the general symptoms of concussion, seems a not improbable supposition; it is not, however, of this class of cases that I would speak at length, but rather of those cases in which a local paralysis of more or less temporary nature accompanies such general symptoms, the pathology being here, I apprehend, a local accumulation of fluid under the arachnoid resulting from rapid exudation at the point of most marked bruising, whether the result of direct violence or of contrecoup. . . . For the unilateral paralysis there seems absolutely no plausible explanation, except the pressure of the fluid, and the relief of paralysis was apparently due to relief of this pressure. . . . This lesion is to be particularly borne in mind in the case of children and young adults, and perhaps in alcoholic patients. In elderly patients the same set of symptoms points more decidedly toward hemorrhage.

Cushing[3] discusses the physiologic effects of acute compression and states:

> We must continually bear in mind the difference between a local and a general increase in tension. Inasmuch as the pressure effects of a local process are greater in its immediate neighborhood than at a distance, and inasmuch also as there is considerable pressure discontinuity between the three intracranial compartments, owing to the fairly rigid partitions formed by the falx and tentorium cerebelli, a local pressure, let us say over one hemisphere, may exceed the local arterial pressure and lead to a local anemia sufficient to throw the adjoining parts of the brain out of function without seriously affecting the other hemisphere or the subtentorial structures, of which the medulla is of prime importance.

And in considering extradural and subdural hemorrhage, he says: "Confusion may arise in certain cases, owing to the fact that acute, traumatic cerebral edema may closely simulate the general pressure phenomena which accompany actual extravasations of blood."[4]

Current authorities on head injuries recognize the existence of states imitating extradural bleeding, but do not lay great stress upon them. Munro[5, 6] remarks:

> In children, hemiplegia and convulsions commonly occur in uncomplicated cerebral oedema. . . . There appears to be a type of malignant and sometimes strictly localized oedema of the brain that will present expansile characteristics. I have usually seen it develop as a postoperative complication.

Rowbotham[7] believes that interval hemiplegias may be caused by edema, among other conditions. Brock[8] writes: "For rare instances of so-called malignant edema which develop rapidly and do not respond to ordinary methods of dehydration and repeated lumbar puncture, exploratory trephine will have to be resorted to, to rule out meningeal hemorrhage." Gross and Ehrlich[9] deny the existence of a process such as that assumed above and say:

> Focal edema of the brain with the development of localizing signs and symptoms which simulate a middle meningeal hemorrhage, has been postulated by numerous observers. This has been used to justify exploration when middle meningeal hemorrhage has been sought and not found, and yet recovery has ensued. It is possible that an extradural clot may be confined over the occipital or occipito-parietal area; more rarely its situation may be far anterior. The improvement following negative exploration can probably be attributed to the decompressive effects concomitant with opening of the dura mater. This serves to prevent fatal cerebral compression. With the tiding over of the critical period, life is sustained, and as the epidural clot slowly reabsorbs, recovery takes place.

At the Rhode Island Hospital, during the past five years, we have treated a total of 8 patients on whom we made the diagnosis of acute focal edema of the brain. The ages varied from ten months to eleven years; we have seen no clear-cut case in an adult. In the same period we have had over 500 children with head injuries, so that the incidence in our experience is low, being well under 2 per cent. Seven of these children were boys. In most cases the child fell and struck his head on the floor or the ground. Linear fracture of the vault, without depression, was present in 3 cases, in 1 of which there was an additional fracture of the maxilla. There was initial unconsciousness in 3 patients. The interval between the injury and the onset of focal signs varied from fifteen minutes to six hours. The focal signs included one-sided reflex changes indicating cortical involvement; Jacksonian convulsive movements and in 1 patient a combination of Jacksonian and generalized convulsions; and one-sided paralyses of varying degrees. Traumatic shock was present in only 2 patients.

It is our practice not to do a lumbar puncture in the presence of shock or when acute extradural or subdural bleeding is suspected, for fear of lessening intracranial pressure and thus increasing bleeding; for these reasons, the cerebrospinal-fluid findings during the active phase of this condition are not available. Punctures done during

or soon after the subsidence of the acute symptoms, however, have shown normal pressures, normal protein levels and the absence of red blood cells in most cases; in 2 patients, the fluid has shown a few red cells, and in 1 it has shown a slight rise in the amount of protein relative to the age, being 36 mg. per 100 cc. in a boy of eleven years. The time needed for the complete disappearance of clinical evidence of the condition has varied from three to twenty-four hours.

We had thus gone along for five years, making this tentative diagnosis as a logical necessity but without actual proof of its existence, until May 1, 1948, when a four-year-old girl was admitted to the hospital. An hour earlier, she had been knocked down by a bicycle and had struck her head on the sidewalk. She became unconscious at once and was carried into the house, where she regained consciousness in a few minutes and vomited. Fifteen minutes later she again lapsed into unconsciousness and began to have convulsive movements of both arms and legs, the left arm and leg being definitely more involved than the right. On admission she was completely comatose, with no apparent response to any stimulus, and had occasional spontaneous movements of the right arm and leg, with no movement at all of the left arm and leg. There were contusion and hematoma of the scalp in the right temporal region and some bleeding from the right ear. Her pupils were moderately dilated, equal and regular, with good reaction to light, and there was a tendency to left-sided deviation of the eyes associated with deviation of the head to the left. The other cranial-nerve functions were grossly normal. The reflexes were overactive on both sides, and there was a questionable Babinski response on the right. The pulse was rapid and of fair quality, and the systolic blood pressure was 130, with no readable diastolic pressure. Breathing was deep and labored and within a few minutes stopped altogether. Artificial respiration was started, and she was given oxygen. We believed that she had a probable compound basal fracture on the right, with some brain contusion, and extradural hemorrhage on the right side. The outlook regarding recovery seemed to be very poor. She was taken at once to the operating room, and a right subtemporal exploration was made without anesthesia. The usual incision emptied out a large scalp hematoma, and showed moderate contusion of the temporal muscle but no apparent fracture line. Removal of the bone showed no extradural bleeding or clot. The underlying dura mater was tense, and there was a slight, bluish discoloration. No free blood or clot was found when the dura was opened. The underlying brain was swollen and edematous, and there were no pulsations to be seen. The dura was opened widely, and the subdural space was explored carefully with a flat, narrow brain retractor so that an area about 10 cm. in diameter was investigated, but no blood or clot was found, and there was no apparent hygroma. After these procedures, the brain seemed to be much less swollen and edematous, and it resumed its normal pulsations. Soon after the dura was opened the child began to breathe of her own accord. The dura was left open, and the wound was closed in the usual way. Within a few hours the girl was fully conscious, oriented, co-operative and apparently well. The positive Babinski response persisted for about twenty-four hours, but after that time no neurologic abnormality could be made out. X-ray films of the skull showed a linear fracture of the frontal bone and the temporal defect left by the operation; no fracture was evident in the cervical spine. A lumbar puncture was done on the fourth day, with entirely normal findings. During her hospital stay the youngster had no remaining evidence of brain damage and was bright and happy. She was discharged on the eighteenth day and has stayed well since that time.

I cannot believe that an extradural clot not found at operation, and lying either well in front of or behind the area explored, as suggested by Gross and Ehrlich,[9] could account for the focal signs shown by this patient; nor can I believe that, with complete recovery within a few hours, there was time for the removal of such a clot by the slow absorption described by them.

The following account, then, probably best explains the pathologic conditions present in this patient. The loss of consciousness coming on at the time of the injury was due to brain concussion, the exact nature of which has not, as yet, been satisfactorily determined. The child recovered from this and then developed signs of compression of the motor cortex characteristic of a rapidly expanding lesion. The three stages of physical compensation, venous congestion and capillary anemia, so well described by Trotter,[10] came on in quick succession. The compression then spread more widely and involved the medullary centers. Swelling and edema of the brain, sufficient to account for capillary anemia, were actually seen in an area where lack of blood supply would cause the focal signs that had been noted. When the pressure was relieved, the vital centers regained their normal functions almost at once; the edema of the brain was seen to subside, and the signs of cortical ischemia were lost in a few hours. It is probable that a process such as this can only be shown in the operating room; even if there should be opportunity for post-mortem examination, it seems unlikely that the condition would last long enough to be evident to the pathologist. I believe that the findings in this last patient indicate the actual occurrence of acute focal edema of the brain.

Summary

Observations made on a series of 7 children, having signs and symptoms strongly suggesting those caused by extradural hemorrhage, but with such rapid and complete recovery without operation as

to cast doubt on this diagnosis, are reported. With particular reference to the time elements present, consideration of various pathologic processes that might be expected to bring about such a clinical picture leads to the conclusion that acute cortical edema, with associated capillary anemia, best explains the condition. This view is supported by the reports and comments of other writers. The finding of visible edema in the region of the motor cortex at operation on an eighth child is reported, and it is believed that this confirms the explanation previously made. In my opinion, acute focal edema of the brain can occur in children with head injuries, and I regard it as a recognizable clinical entity.

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EXTRARENAL AZOTEMIA

Report of a Severe Case with Recovery

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AS FAR back as 1912 Froin and Marie[1] reported the occurrence of prerenal azotemia in choleriform enteritis. Similar observations of prerenal azotemia were made by Nobécourt, Bidot and Maillet[2] in gastrointestinal disturbances in infancy in 1912 and by Tileston and Comfort[3] in intestinal obstruction with vomiting in 1914. Only in recent years, however, has this condition been more completely understood.

The characteristic picture of extrarenal azotemia is that of renal failure without actual renal disease or of renal disease not sufficient to explain the signs of renal failure present. The more important signs of extrarenal azotemia include an elevation of the nonprotein nitrogen of the blood, uremic odor of the breath, dehydration, loss of electrolyte (particularly the chloride ion), and oliguria or anuria. The eyegrounds, on the other hand, appear normal, the blood pressure is not elevated, and the specific gravity of the urine is not markedly diminished, if at all lowered. Casts, red cells and white cells may be present in the urine, but these characteristically disappear.

The conditions in which extrarenal azotemia may occur are numerous, the following being mentioned by Jeghers and Bakst[4]: coronary thrombosis; alkalosis; pyloric obstruction; peritonitis; liver-kidney syndrome; yellow fever; gastrointestinal hemorrhage; postoperative complications; congestive heart failure; reaction to transfusion and intravenous therapy; Weil's disease; Addison's disease; pneumonia; allergy; diabetes mellitus; shock; acute pancreatitis; diarrheal disease; heat cramps; drug intoxication; and burns.

In 1941 Garis[5] reported a case of prerenal uremia due to papilloma of the rectum. In the same year Layne and Moir[6] reported several cases of extrarenal uremia, an unusual one being a case of tabetic crisis with persistent vomiting. O'Donovan,[7] in 1944, described 2 cases of extrarenal azotemia resulting from pyloric obstruction.

It is believed that the elevation of the nonprotein nitrogen of the blood in prerenal azotemia originates from one or both of two sources: an impaired elimination of the nonprotein nitrogenous products of the blood; or an increased production of these products. Jeghers and Bakst[4] described the following basic causes of extrarenal azotemia: a drop in blood pressure; hypochloremia and hyponatremia; dehydration; liver damage; and protein catabolism. All factors need not be present in the same patient, but sometimes a combination of conditions or even a single one is sufficient to produce prerenal azotemia.

Fishberg[8] considers a similar group of factors: hypochloremia; low arterial pressure; toxic nephritis; and alkalosis. Furthermore, Fishberg believes that the primary pathogenic factor in most — if not all — cases of prerenal azotemia with impaired renal function is a diminution of blood flow through the kidneys. This appears to be true of the causes enumerated by Jeghers and Bakst.[4]

A drop in systemic blood pressure reduces the blood flow through the glomeruli, diminishes the urine volume and, if of sufficient magnitude, results in azotemia. Hypochloremia and hyponatremia

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are generally related to excessive loss of fluid (as in persistent vomiting, diarrhea or perspiration). With the resultant dehydration, there is a diminished blood volume, hemoconcentration, reduced blood flow through the glomeruli, and impaired glomerular filtration.

According to Jeghers and Bakst,[4] patients with azotemia and liver damage have had inadequate study for hypochloremia, hyponatremia and low blood pressure to determine whether liver damage per se produces azotemia.

Fishberg[9] believes that protein catabolism increasing the blood nonprotein nitrogen occurs if there is associated impaired function. He cites the example of urea given to a patient with normal kidneys in amounts exceeding that of accelerated protein catabolism without producing an increase in urea of the blood. His final conclusion is that "when considerable azotemia is present. . . renal excretion is subnormal."

In the review of the factors enumerated by Fishberg[8] presented above, hypochloremia and low arterial pressure were discussed. The conception of toxic nephritis is a hypothetical one. Damage to the kidneys, as through acute infections, is supposed to occur by circulating toxins in the blood. These have not been demonstrated, and, furthermore, the response to hydrotherapy and electrolytic therapy is difficult to explain on this basis. Alkalosis is frequently associated with vomiting, and in those cases the mechanism could be explained by dehydration.

The common denominator, then, in the pathogenesis of prerenal azotemia appears to be diminished blood flow through the kidneys, which fortunately is reversible in many cases, provided treatment is started early. On the other hand, if treatment is instituted too late or is inadequate, irreversible renal damage may occur.

In the following case the signs of severe renal failure were caused by the mechanism described above. After intensive therapy the renal function returned to normal.

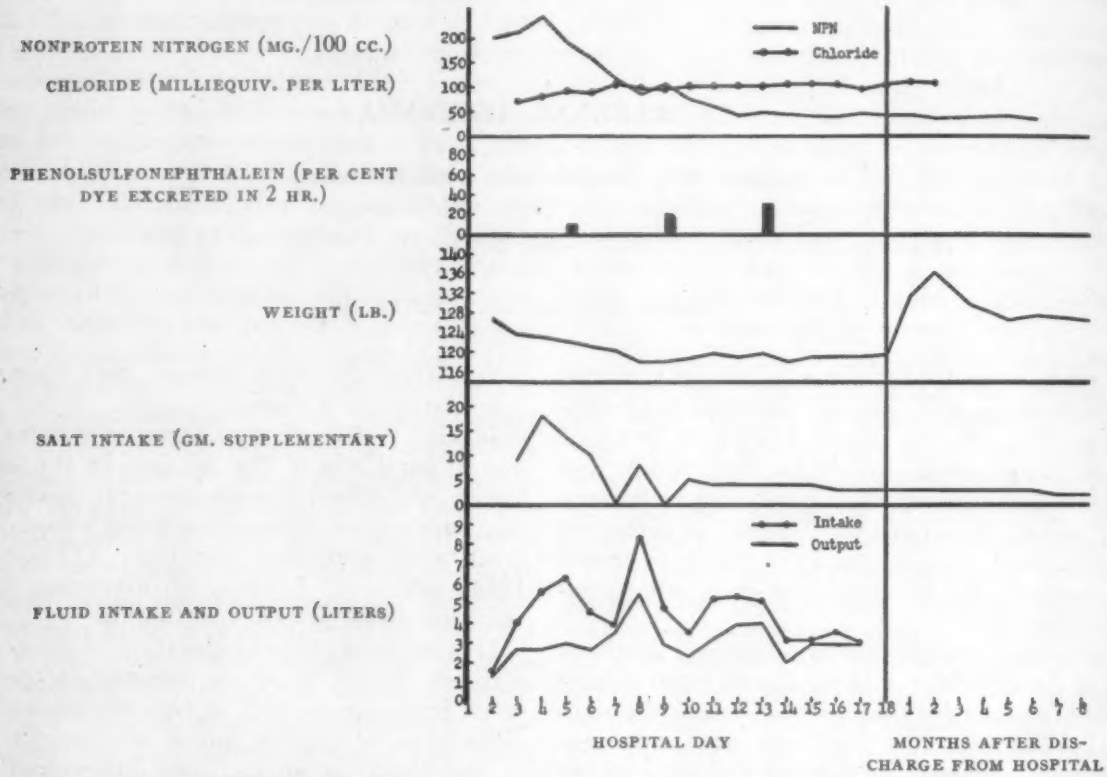

FIGURE 1. *Course of the Blood Nonprotein Nitrogen and Chloride, Phenolsulfonephthalein Excretion Test, Body Weight, Supplementary Salt Intake and Fluid Intake and Output in the Hospital and during the Eight Months' Follow-up Period.*

CASE REPORT

J. D., a 37-year-old rubber-factory worker, was admitted to the hospital on January 26, 1947, with the chief complaint of abdominal pain of 15 days' duration. While he was at work on the night shift in the hot and moist environment of a rubber factory, severe frontal headaches followed by a chilliness and continuous anorexia, and nausea without abdominal pain developed. He continued to work, but on the following morning he vomited material that was not grossly bloody. Shortly afterward a sharp pain appeared in the lower abdomen near the midline, shifting at times to the epigastrium but with no relation to meals. There was also inconstant and transient pain in the lumbar region, radiating anteriorly to the lower abdomen. The patient remained in bed at home, but his condition became worse: the abdominal pain became more severe, and the nausea, vomiting and headache persisted unabatingly. Eight days before admission the patient summoned his family physician,

who believed he had a peptic ulcer and prescribed a regime of milk, cream and "amphojel." Nevertheless, the symptoms continued, so that hospitalization was finally recommended. There was no history of hematemesis, jaundice, melena, clay-colored stools, constipation or diarrhea.

The patient had noted bleeding from the gums for the past week, and on the day of admission, he had an episode of epistaxis, which stopped spontaneously. Although there was no history of dysuria or hematuria, he had usually drunk about 3 quarts of water while at work for the past 1½ years. However, his fluid intake was markedly reduced after the onset of the vomiting. Furthermore, according to the patient's wife, severe oliguria had begun 10 days before admission, but the exact degree of the oliguria could not be ascertained.

The past history gave no evidence of cardiac or renal disease, scarlet fever or frequent sore throats.

Physical examination revealed a fairly well nourished and well developed man, moderately dehydrated and drowsy, lying flat in bed without dyspnea or cyanosis and not answering questions readily. There was a pterygium of the left eye and a subconjunctival hemorrhage below the right iris. Funduscopic examination disclosed no choking of the disks and no hemorrhage, exudate or spasm of the arteries. There were dried blood clots in the right naris, and generalized gingival bleeding, with reddish discoloration of the tongue. No abnormal findings were present in the chest. The blood pressure was 144/90. On deep palpation there was slight tenderness in the epigastrium and moderate tenderness at both costovertebral-angle areas. Rectal examination revealed no abnormal masses. Although the gloved finger showed no evidence of gross blood, the specimen yielded a ++ guaiac test for occult blood.

The initial impression was that the patient had a bleeding peptic ulcer and possibly a vitamin C deficiency, or some form of blood dyscrasia. Therefore, he was placed on a regimen of Meulengracht diet, "gelusil," tincture of belladonna and large doses of vitamins.

On the 2nd hospital day the patient continued to be drowsy and to complain of pain in the lumbar region, radiating to the lower abdomen. The prothrombin time was 16 seconds (normal, 17 to 22 seconds); the bleeding time was 2 minutes and 7 seconds, and the clotting time, 4 minutes and 1 second. The red-cell count was 5,050,000, with a hemoglobin of 15 gm., and the white-cell count 11,300, with a normal differential count. The blood nonprotein nitrogen was 200 mg. per 100 cc. Urinalysis showed a trace of albumin with 8 to 10 white cells and 30 to 40 red cells per high-power field in the sediment. In view of the clinical picture and laboratory findings, the plan of treatment was changed to increase substantially the daily fluid and electrolyte intake.

Figure 1 demonstrates the hospital course, showing how the blood nonprotein nitrogen rose to 245 mg. per 100 cc. and then fell gradually to normal, remaining so. The fluid intake was entirely by mouth except on the 3rd hospital day, when 1000 cc. of 5 per cent glucose in physiologic saline solution and 1500 cc. of 5 per cent glucose in distilled water was given intravenously. The carbon dioxide combining power fell from 32.6 milliequiv. on the 3rd hospital day to 23.0 milliequiv. per liter (normal, 23 to 30 milliequiv.) on the 8th hospital day. Subsequent urinalyses showed specific gravities in the realm of 1.010 with traces of albumin, a few white and red cells and occasional granular casts. The blood pressure remained constant at about 134/84 throughout the hospital course.

An electrocardiogram on the 4th hospital day showed a sinus bradycardia at a rate of 50 per minute, with left-axis deviation, but a second tracing 13 days later was entirely normal. On the 5th hospital day the serum protein was reported as 7.2 gm., the albumin as 4.6 gm., and the globulin as 2.7 gm. per 100 cc., with an albumin-globulin ratio of 1.8. A barium enema on the 7th hospital day showed the barium to pass freely to the cecum. There was no evidence of carcinoma or diverticulitis. A chest x-ray film disclosed no abnormalities of the heart or lungs. On the same day a stool examination demonstrated no ova, parasites or blood. By the 9th hospital day the patient had become stronger, with improved appetite, so that he was allowed to be ambulatory. An intravenous pyelogram on the 12th hospital day showed normal-appearing calyxes, pelves and ureters and normal excretory function. The blood phosphorus was reported as 4.1 mg. per 100 cc. on the 16th hospital day, and an upper gastrointestinal series was entirely normal.

The patient was discharged on the 18th hospital day on a regime of supplementary salt of 4 gm. and 10 glasses of water a day. His follow-up course in the outpatient department was uneventful (Fig. 1). Urinalyses done 2, 4 and 6 months after discharge revealed clear urine with specific gravities of 1.025, 1.020 and 1.018 respectively.

Discussion

The unusual feature of this case was the extremely high nonprotein nitrogen that fell from 200 to 42.5 mg. per 100 cc. after ten days of intensive electrolytic therapy and hydrotherapy. At no time during this treatment could the output be considered low. The significance of alkalosis could not be ascertained altogether. While the patient was in the hospital, alkalosis was never more than slight. Its magnitude before admission, on the other hand, might have been more marked, but unfortunately was not known. The blood pressure remained constant around 134 systolic, 84 diastolic. It never reached the low levels of traumatic shock or severe transfusion reaction.[10] The return of renal function to normal was shown by an excretion of 60 per cent of phenolsulfonephthalein in two hours (compared with 20 per cent excretion of the dye eight days previously) and by the normal excretion of dye in the intravenous pyelogram four weeks after the onset of the illness. Furthermore, the sustained normal nonprotein nitrogen and the specific gravity of 1.025 and 1.020 two and four months after the onset of illness helped to substantiate the return of renal function to normal.

The rationale in therapy was to restore the continued loss of fluids and electrolytes as soon as possible by the increased fluid and sodium chloride intake by mouth and by infusions of glucose and physiologic saline solution intravenously. In this way hemoconcentration and dehydration were reduced, blood flow through the glomeruli increased and normal renal excretion restored.

Summary

The occurrence and pathogenesis of extrarenal azotemia are discussed.

A case of severe prerenal azotemia preceded by dehydration and moderate intake of alkalis, and followed by return of renal function to normal after intensive electrolytic treatment and hydrotherapy, is presented.

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MEDICAL PROGRESS

ANTIBACTERIAL CHEMOTHERAPY*

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IT IS an interesting commentary on one man's impact upon the growth of scientific medicine that a review of a rapidly expanding field, written thirty-five years after his death, should comprise a mere addition of details to the broad guiding principles he established. In this thirteenth year of the clinical use of sulfonamides, the seventh of penicillin and the fourth of streptomycin, it seems entirely appropriate to introduce the discussion by a restatement of the fundamentals upon which Ehrlich[1-3] founded the science of chemotherapy.

As intended by its author, the word "chemotherapy" means the treatment of parasitic disease by direct chemical attack upon invading organisms — viruses, fungi, bacteria, spirochetes, protozoa or helminths. In my opinion extending this meaning to include the treatment of a variety of pathologic states (for example, "chemotherapy of heart disease") blurs a distinction that is as fundamental today as when it was first introduced by Ehrlich. It is precisely the killing of pathogenic forms of life with a *minimum* of effect upon the tissues and physiologic processes of the host that is the unique goal of chemotherapy. All drugs that may be employed to this end are referred to below as "chemotherapeutics,"‡ arbitrary distinctions between molecules produced in the laboratory and those (the so-called antibiotics[6]) whose synthesis the organic chemist has not yet achieved being avoided.

Chemotherapeutics do not act primarily upon the host but rather combine chemically with certain systems of parasitic organisms. Ehrlich showed that affinity for a parasite often requires a very exact structure in a drug, whose entire potency may hang upon addition or removal of a single atom. He summarized the high degree of specificity of this combination in his well known "receptor" or "side-chain" hypothesis.[7] From the concept that chemotherapeutic action is fundamentally a chemical combination came two important corollaries: that the basic phenomena should be amenable to study in the isolated parasite, in vitro, wherever the organism could be grown; and that stoichiometry or mass law relations, or both, must apply as in any chemical reaction — that is, for a given system a definite total dosage or concentration, or both, will be required for complete combination with the organisms.

Ehrlich early realized that although a great many drugs were effective at some concentration in vitro, toxicity for the host might prevent their systemic utilization. When he had shown, however, that affinity for parasite (parasitotropism) and for host tissues (organotropism) by no means went hand in hand, the way was opened for molecular modifications that would increase the former or decrease the latter affinity. Ehrlich's view that drugs also combined with tissue cells through receptor side chains was an adequate expression of the facts at a time when the specificity of protein interactions was still dimly understood. Today the same views could be reformulated in terms of enzyme-mediated steps in metabolic processes — some playing a role in both parasite and host, and others being unique to each organism or host tissue.

The practical implications of specific and differential toxicity to parasite and host were summarized in Ehrlich's *chemotherapeutic ratio*.[1] The criterion of usefulness of a chemotherapeutic is not in its absolute molar potency against the parasite but only in the *ratio* of dose first producing toxic effects in the host to that required to kill the parasite. *Comparisons between chemotherapeutics on a gravimetric basis are without significance in foretelling their possible clinical value.*

Thus, Ehrlich's work led to a clearly formulated approach to the development of agents useful in clinical chemotherapy. The first main step was to discover by isolation or synthesis compounds that would effectively kill the parasite at some reasonable concentration in vitro, and to study the mechanism of interference by such agents with the metabolic pathways. The second was to select drugs that would yield a satisfactory chemotherapeutic ratio — that is, agents sufficiently nontoxic to be of clinical promise — and to investigate the means of reducing toxicity, by modification of structure or otherwise. The third was to work out the practical pharmacodynamics — that is, the fate of the drug in the body — to determine the optimal dose, route and frequency of administration, and other special methods for bringing the drug into full chemical combination with the parasite,

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‡The word appears in the designation of a Committee of the National Research Council[4] during the war years and has been advocated more recently by Dr. B. D. Davis.[5]

in whatever tissues it might be found. The fourth was to apply the agent in controlled clinical studies and to evaluate by sound statistical methods the results of therapy.

What has thus far been said applies to all chemotherapy. The following sections review recent advances in understanding and employment of chemotherapy directed in particular against bacterial infections. The four steps outlined above serve as framework for the discussion of chemotherapeutics in general use, after which some that are presently in the developmental stage are briefly reviewed.

In Vitro Studies and Mechanism of Action

Prior to 1935 a great number of inorganic and organic substances were known to inhibit the growth of micro-organisms or to kill them. Metallic ions, phenols, aliphatic alcohols, organic acids, dyes, oxidizing agents, soaps and detergents are classes of compounds displaying an antiseptic or, at higher concentrations, a disinfectant action. These agents vary considerably in specificity for different organisms, the gram-positive group being, in general, most readily attacked. Logarithmic killing curves are obtained with adequate concentrations, and the death rate is critically related to concentration. The deficiency of all these substances lies in their indiscriminate affinity for a multitude of host proteins along with those of pathogenic organisms, a circumstance that led to the vague and inexact descriptive term "general protoplasmic poisons." Their unfavorable chemotherapeutic ratio restricts their use (with the exception of a few dyes and organic acids) to topical applications and sterilization of inanimate objects.

Sulfonamides

Domagk's introduction of prontosil[8] and the subsequent use of the sulfonamides (Fig. 1) was remarkable not because this class of compound was more potent than the antiseptics in inhibiting bacterial growth. On the contrary, comparable concentrations of phenolic compounds and mercuric chloride accomplish the same end-result, whereas the newer cationic detergents are effective at less than 0.5 mg. per 100 cc.[9-13] The remarkable fact was that the effective sulfonamide concentrations should be tolerated in body fluids without prohibitive toxicity. Thus was the era of systemic antibacterial chemotherapy inaugurated.

The sulfonamides are often stated to be purely bacteriostatic. There is clear evidence, however, that although low concentrations inhibit growth, higher concentrations cause a progressive reduction in the viable count.[14] The bacteriostatic effect is not immediate in onset but occurs only after several cell divisions in the presence of the drug. If nongrowing organisms are suspended in a sulfonamide solution and then removed and placed in a normal growth medium the drug is without effect.[15] The bactericidal action likewise appears only in a medium favoring growth. The respiration of nongrowing cells is not affected,[16, 17] but the additional respiration entailed in growth is inhibited.[16, 18] The suggestion that bacteriostasis is secondary to this inhibition of respiration is neither more nor less valid than the view that the latter is the result of the former.

The inactivity of the sulfonamides in the presence of pus and tissue extracts soon led to the isolation of para-amino-benzoic acid (PABA), which competitively antagonizes sulfonamide action.[19, 20] The idea that these drugs blocked the normal bacterial

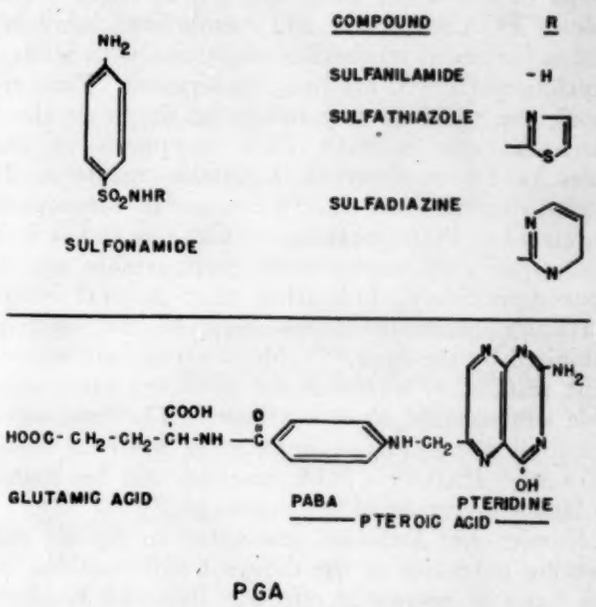


Figure 1. *Structural Formulas of Some Sulfonamides and Pteroylglutamic Acid (Folic Acid).*

utilization of PABA[15] gave impetus, through the Woods–Fildes theory[19, 21, 22] to the whole fruitful study of biologic antagonisms.[23, 24] It was finally confirmed by the discovery of folic acid[25] (pteroylglutamic acid, PGA) as an essential substrate in the growth of many bacteria. This compound (Fig. 1) is a conjugated molecule containing one residue each of glutamic acid, PABA and a base (pteridine). That sulfonamides prevent the incorporation of PABA into the PGA molecule now seems established beyond reasonable doubt. Organisms that are entirely independent of the need for PGA are not sensitive to sulfonamides. Organisms that require *ready-made* PGA as a "growth factor" are also insensitive to sulfonamides, since they lack the metabolic step upon which the drug acts[26]; PGA analogues, however, inhibit their growth.[27, 28] Sulfonamide-sensitive organisms are evidently those that must form their own PGA from PABA. Sulfonamide growth inhibition in such organisms is relieved *either* by PABA *or* by PGA

itself. As one might expect, the antagonism produced by the former is competitive, growth inhibition depending upon the ratio of PABA to sulfonamide. On the contrary, in the presence of PGA, sulfonamide is without effect, regardless of concentration, within limits. The antagonisms cited here have been demonstrated not only for bacteria but also for psittacosis virus, whose growth on embryonated eggs is inhibited by sulfonamides and restored by PABA or PGA.[29]

This scheme explains the characteristic lag of several cell divisions before growth inhibition by sulfonamides occurs; it is assumed that PGA stores are being exhausted during this period, the synthesis of new PGA being blocked at once.[22] The role of PGA in growth and metabolism, however, and in particular its curious connection with human erythropoiesis[30, 31] are not understood. Furthermore, the relations may not be as simple as these generalizations indicate, since exceptions to the rules have been observed in certain organisms. It is also demonstrated that a number of compounds unrelated to PGA (methionine, xanthine and serine) are capable of antagonizing sulfonamide action noncompetitively, indicating that several enzymatically controlled steps may be successively inhibited by the drug.[32-36] Moreover certain important respiratory enzymes are inhibited at reasonable sulfonamide concentrations.[37] The best summary of the evidence implicating systems other than the PABA –> PGA reaction can be found in Henry's[38] review of five years ago.

Kumler and Daniels[39] attempted to explain the varying potencies of the different sulfonamides on the basis of resonance effects. Bell and Roblin[40] made a similar correlation between pK and potency, and made the interesting prediction that sulfadiazine (Fig. 1) already possessed optimal antibacterial activity and could only be improved upon with respect to other pharmacologic properties (such as toxicity). This prediction was apparently correct. Of the newer systemic sulfonamides only sulfamerazine (monomethyl sulfadiazine) and sulfamethazine (dimethyl sulfadiazine) have merited widespread clinical trial, and neither is intrinsically more potent than sulfadiazine. Nor, in general, have various sulfonamides displayed appreciable differences in bacterial affinities (provided only that the para-amino group remain free), molecular changes in the N_1 substituent serving to modify quantitative rather than qualitative antibacterial properties.

Gramicidin, Tyrocidine and Tyrothricin

From a chronologic point of view the next potential chemotherapeutics to appear were tyrocidine and gramicidin, which Dubos[41] obtained from *Bacillus brevis* by isolation from the crude mixture, tyrothricin. These compounds were shown to be bactericidal, preferentially against gram-positive forms, and also to display a hemolytic action that, among other toxic features, prevented their systemic use.[42] Gramicidin (or tyrothricin) is still employed to some extent in the treatment of surface infections caused by gram-positive cocci. Tyrocidine acts, in every respect, like a disinfectant; it markedly inhibits cell respiration and disrupts the bacterial cell wall. Gramicidin, on the other hand, inhibits growth, does not lyse bacteria and stimulates the oxygen uptake of nongrowing cells.[43] In view of these differences it is interesting that they should have become prototypes of the large group of substances now classed as "antibiotics" — a fine illustration of the fact that biologically produced antibacterials as a group have no unique mechanism of action.

Gramicidin and tyrocidine have proved unusually interesting from the structural standpoint. They are cyclic peptides containing a number of residues of various amino-acids, some being of the unusual d- configuration.[42] Investigation by the newer technics of counter-current distribution and paper chromatography has revealed at least four different gramicidins.[44] The major component contains l-tryptophane, d-leucine, d,l-valine, l-alanine, l-glycine and ethanolamine. The others differ in respect of one or more amino-acids. The minimal molecular weight appears to be approximately 8700, representing about 70 residues. Tyrocidine yields, on hydrolysis, ornithine, proline, valine, leucine, tryptophane, tyrosine, aspartic acid and glutamic acid of the usual configurations, and d-phenylalanine. Gramicidin-S consists of but five amino-acids, l-ornithine, proline, valine, leucine and d-phenylalanine.[45] As pointed out below, these unusual polypeptide arrangements prove to be typical of a number of naturally occurring antibacterial substances. The mechanisms whereby compounds of this type produce growth inhibition in one case and lyse a cell wall in another and the significance of the ever-present d-amino-acid, remain equally obscure.

Penicillins

The advent of penicillin[46, 47] provided a clinical weapon of unsurpassed excellence not, again, because of its higher molar potency, but because its toxicity is negligible even at doses fantastically higher than those required for minimal antibacterial effect. The need to produce the drug biologically and in vast quantities to meet war requirements stimulated considerable research into its structure and the optimal conditions for its synthesis by the mold.[48] The first line of endeavor led to the surprising result[49] that the drug is (or appears to be) a curious ring condensation of two amino-acids — alanine and beta-dimethyl-cysteine (Fig. 2). The structure was later confirmed by a token synthesis,[50] but the mold is still more efficient than the chemist

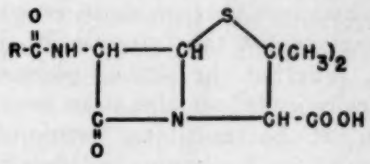
at this task. The various penicillins* were shown to differ in the substituent acid coupled to the alanine amino-group.[51, 52] It was demonstrated that the type of penicillin produced varied with the substrate supplied — phenylacetic acid, for example, being coupled to yield benzyl penicillin. When isotopically labeled phenylacetylvaline was supplied, only the phenylacetyl portion was incorporated, demonstrating that the unique portion of the penicillin molecule is synthesized separately and coupled as a unit to any one of a number of organic acids.[53] The ring-condensed amino-acid portion can be synthesized, at least in part, from simple materials since labeled sulfur, supplied as sulfate, is recovered quantitatively in the penicillin molecule.[54]

The penicillins are moderately strong acids whose sodium, potassium, calcium or other salts may be used therapeutically. The carboxyl group must be free and ionized, esterification destroying the entire activity of the molecule.[55] Two comprehensive reviews of penicillin chemistry have recently appeared.[56, 57]

A remarkable preferential affinity for gram-positive organisms and spirochetes is shared by all the penicillins. That there are quantitative differences is established; p-hydroxybenzyl penicillin (X), for example, is more potent than benzyl penicillin (G) against most organisms.[58-61] But the general pattern of affinities is the same, and the differences have not appeared substantial enough to warrant large-scale commercial production of other types than penicillin G, which is now available in pure crystalline form, requires no refrigeration and is of standard potency.[62] In accordance with established procedure the *unit* should long since have been dropped.

An interesting sidelight on the purification of penicillin is the finding by Hobby and her collaborators[63] that in some respects the protective action of crystalline benzyl penicillin is inferior to that of the cruder material in experimental animal infections. It has been suggested that the original mixture contained impurities of an antitoxic nature,[63, 64] that phenylacetic acid, which is known to potentiate penicillin action, was the responsible agent,[65] or that specific metabolic inhibitors were present.[66]

Penicillin is bacteriostatic in threshold concentration and bactericidal in higher concentration.[67-69] Neither effect is observed unless cells are growing,[14, 67] and the killing action is most pronounced against young, rapidly growing organisms.[14, 70] It is enhanced by substances and conditions that promote growth.[70] Cells exposed to penicillin show characteristic morphologic abnormalities, notably giant forms that fail to divide.[14, 71] It had been thought that the bactericidal effects of the drug resembled those of some of the common disinfectants. But Eagle[72, 73] has recently shown, confirming earlier work by Hobby,[67] that the rate of killing does not follow increasing concentration beyond a certain point. Unlike disinfection, therefore, the bactericidal effect seems to depend upon the degree of blocking of a vital system whose complete saturation results in a constant maximal death rate. The onset of bacteriostasis is preceded by a short lag period,[14] and a prolonged lag is observed before growth resumes when organisms are transferred to fresh medium after brief exposure to the drug.[74-76] Respiration is not inhibited except under conditions favorable to growth.[77, 78] These findings are all so similar to those obtained with the sulfonamides that it is difficult to substantiate the earlier consensus that the action mechanisms of penicillin and the sulfonamides differed fundamentally from one another.



PENICILLIN

TYPE	R	
G	BENZYL	$C_6H_5CH_2-$
X	P-HYDROXYBENZYL	$HOC_6H_4CH_2-$
F	PENTENYL	$CH_3CH_2CH=CHCH_2-$
DIHYDRO-F	N-AMYL	$CH_3CH_2CH_2CH_2CH_2-$
K	N-HEPTYL	$CH_3CH_2CH_2CH_2CH_2CH_2CH_2-$

FIGURE 2. *Structural Formulas of the Principal Naturally Occurring Penicillins.*

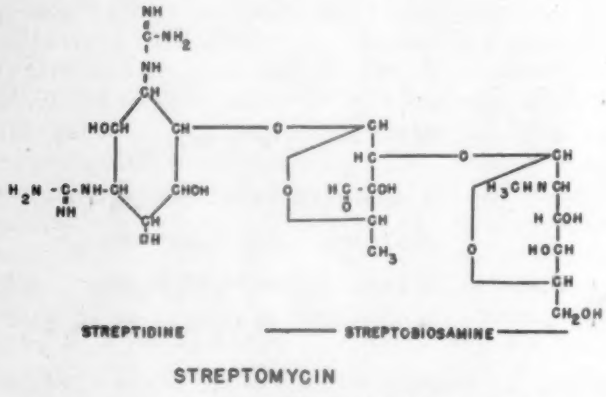
The ingenious studies of Pratt and Dufrenoy,[65, 79-81] who investigated the chemical reactivities of various portions of typical penicillin agar assay plates, showed that the drug promotes a shift of -SH to S-S and of aldehyde or enol to ketone, suggesting a primary interference with oxidation-reduction systems. These workers demonstrated that the zone of increased growth at the margin of an inhibition zone, corresponding to just subthreshold penicillin concentration, was the area in which the biochemical shifts described were most active. It is significant that by their methods the authors were unable to show any qualitative differences in the action upon "sensitive" gram-positive and "insensitive" gram-negative organisms, provided only

*As is customary, the word penicillin, unless qualified, is used here to denote penicillin G — benzyl penicillin.

that a high enough penicillin concentration were used to inhibit growth of the latter. This points up the fact that sensitivity to most chemotherapeutics is relative, expressed in terms of a threshold concentration for growth inhibition.

One of the incidental findings in these experiments was the specific action of cobalt in enhancing penicillin activity in vitro[81] and in experimental pneumococcal infection in mice.[82] This may be another example of the penicillin-enhancing properties of substances that promote growth, in view of the recent report that vitamin B_{12} is a cobalt complex.[83] Whether the curious phenomenon will prove clinically useful remains to be seen.

Penicillin at bacteriostatic concentrations inhibits ribonuclease,[84] mononucleotidase[85] and phosphatase[86] (not confirmed by a second group of investigators[87]). Specific inhibition of other metabolically important enzymes has not been demonstrated.



STREPTOMYCIN

FIGURE 3. *Structural Formula of Streptomycin.*

Although a number of compounds are capable of antagonizing penicillin action,[88, 89] none have been shown to play a metabolic role analogous to that of PABA in the antagonism of sulfonamides. Penicillinase, an enzyme destroying the drug and produced by some bacteria,[90, 91] is connected with one type of resistance (as mentioned below), and its elaboration by *Escherichia coli* probably explains the disappearance of a major portion of orally administered penicillin. But the enzyme clearly bears no relation to the fundamental action mechanism. Its incorporation into bacteriologic mediums to eliminate the penicillin present in body fluids taken for culture has become routine.[92]

A remarkable series of studies by Gale and his collaborators[93] has revealed an entirely new and fascinating aspect of the problem of mechanism of action. They have shown that gram-positive *but not gram-negative* organisms are capable of actively taking up and concentrating free glutamic acid and lysine from the environment, and that this process is mediated by components of the cell wall.[94, 95] The sharp distinction between the gram-positive and gram-negative groups is probably connected with the presence or absence of the magnesium-ribonucleate complex shown to be responsible for positive gram-staining properties.[96-99] Penicillin acts upon the cell wall to prevent the amino-acid uptake, but only when the cells have grown in the presence of the drug. Penicillin is without effect upon the glutamic acid uptake of respiring, nongrowing cells.[100] Variants becoming resistant to penicillin have been shown to assume gram-negative properties,[101, 102] at the same time acquiring the ability to grow and reproduce without assimilating and concentrating glutamic acid, and thus, by an alternate metabolic pathway, becoming independent of the penicillin action. Indeed, it has been shown that such resistant forms are able, like most gram-negative organisms, to synthesize a number of amino acids.[102-104]

Tyrocidine, phenol and the detergents appear to act by a simple disruption of the cell wall[10] (demonstrable in electron micrographs[105]) so that glutamic acid and other soluble constituents leak out. Triphenylmethane dyes were shown to block the *internal* utilization of glutamic acid in resting as well as growing cells, from which it is concluded that the interference is with a phase of the amino-acid metabolism not involved in growth and protein synthesis.[106] One such reaction blocked by triphenylmethane dyes is the formation of glutamine through phosphorylation of glutamic acid in the presence of adenosine triphosphate (ATP).[93] It was quite clear that neither penicillin nor sulfathiazole interfered with this utilization of glutamic acid, even under conditions of growth.

Sulfathiazole did not prevent glutamic acid assimilation by the cell wall. *In growing cells only*, it did block the internal utilization of glutamic acid. This blocked metabolism, however, was quite distinct from that described above, since it involved the condensation of glutamic acid residues into peptide or protein structures.[17]

Streptomycin

Streptomycin owes its unique position to its preferential selectivity for gram-negative and acid-fast organisms. It is unquestionably bactericidal for growing cells,[107-109] and unlike that of penicillin, the killing rate increases as the concentration is raised.[110] Strauss[111] asserts that the drug is bactericidal even for resting cells, but at a higher threshold; this suggests a different action mechanism from penicillin, which was only effective against growing cells, but conditions have not been made sufficiently comparable to settle this point unequivocally. The same investigator, and others,[109, 111] report morphologic abnormalities occurring at bacteriostatic levels.

To the pharmacologist it is of some interest that streptomycin is a glycoside (Fig. 3).[112] Like other

drugs of this class the hydrolyzed residues display little if any of the original activity. The significance of the hexose and glucosamine components[114] is not clear, nor the meaning of the similarity of the streptidine portion[115] to the B vitamin inositol. From the observed increase in potency with pH it is inferred that the basic guanido groups of streptidine confer optimal properties in their uncharged state.

It has been observed[116] that streptomycin can precipitate as a complex with desoxyribosenucleic acid (DNA), a fact that raised interesting possibilities in view of the intimate connection of the latter compound with protein-synthetic processes. Other investigators,[117] however, showed that the complex actually dissociated at physiologic saline concentrations; that phosphate had opposite actions on the DNA-streptomycin complex and the antibacterial affinity of the drug; and that the enzyme desoxyribonuclease, which depolymerizes the complex, has no effect upon streptomycin potency. These facts call the significance of the action of the drug upon DNA into considerable question, the investigators also pointing out that viruses of the psittacosis-lymphogranuloma group, which are rich in DNA, are also relatively insensitive to streptomycin. Complex formation with ribonucleate has also been reported,[118] and is discussed below.

Like penicillin, streptomycin is antagonized by a number of compounds. Anaerobic conditions or the presence of glucose reduces its potency but this is primarily the result of increased acidity.[119, 120] Bivalent cations (magnesium, calcium and barium) and certain anions (phosphate, sulfate, citrate and tartrate) are competitive antagonists.[117] Ascorbic acid and sulfhydryl compounds like cysteine and thioglycollate are also antagonists[120-123]; whether they act by lowering the redox potential of the medium is not clear, but such an interpretation would be consistent with the greater sensitivity of aerobic than anaerobic bacteria.[124, 125]

Along these lines, Cavallito and his co-workers[126, 127] have shown that penicillin, streptomycin and other complex antibacterial agents are capable of combining with certain thiols in isolated chemical systems. Whereas mercuric ion combines rather indiscriminately, penicillin and streptomycin are highly selective for –SH groups surrounded by proper reactive neighboring groups (for example, an amino-group separated from –SH by an exact number of carbon atoms). Once formed, the mercury complexes are readily reversed by other reactive thiols, but the penicillin and streptomycin complexes are not. The data are advanced in support of the view that combination with thiol groups mediates the antibacterial action of these drugs,[128, 129] a suggestion that is consistent with the findings of Pratt and Dufrenoy. The interesting observation has been made[130] that penicillin can be considered a structural analogue of glutathione, whose function is thought to involve maintenance of reduced sulfhydryl groups.

Fitzgerald and Bernheim[131, 132] reported that the oxidation of benzoic acid by the tubercle bacillus is selectively inhibited by bacteriostatic concentrations of streptomycin and that this does not occur in resistant strains. Green, Iverson and Waksman[133] demonstrated interference by pyruvate or fumarate with streptomycin activity, an antagonism that is not shared by a number of other organic compounds. Rhymer et al.[134] showed that the structural analogue, lipositol, is a streptomycin antagonist. But none of these phenomena were shown to be related in a definite way to the action mechanism of the drug.

As Gaddum[135] has pointed out, there are two sharply defined categories of drug antagonism — one drug may compete with another for a receptor site, or one drug may form a chemical complex with another and thus prevent its combination (or if the affinity is great, remove it from combination). The PABA-sulfonamide antagonism is obviously of the first type and is thereby directly concerned with the drug's mechanism of action. A simple example of the second type is the neutralization of cationic by anionic detergents.[136] Antagonisms of this kind can give insight into the intimate manner of combination with cell receptors only by inference and deduction. Thus the demonstration that a sulfhydryl compound combines with a chemotherapeutic, or even reverses its action on the bacterial cell, suggests, *but does not prove*, that the drug acts by combining with bacterial –SH groups.[137] It must be concluded that, with the possible exception of the benzoic acid results, the work cited has yielded no proved antagonists of the first type. Consequently experiments with antagonists have as yet contributed little definitive information to knowledge of the sites and mechanisms of combination of penicillin and streptomycin with bacterial cells.

Mechanisms of Antibacterial Action

Broadly speaking, bacterial growth can be interrupted by interference with two main pathways: catabolic reactions yielding the energy required for protein synthesis; and the anabolic, synthetic processes themselves. To these should be added the special mechanisms that control cell fission and the reduplication of genetically functioning nucleoprotein.

The bacteriologic criterion of death is an irreversible inability to reproduce when the cell is introduced into fresh medium suitable for growth. It has proved difficult to make a sharp distinction between bacteriostatic and bactericidal action. If growth inhibition is prolonged, a logarithmic death phase sets in; indeed, a progressive loss of viability is observed even in a normal culture in the stationary phase, when growth has ceased.[138] The reproductive mechanism in bacteria appears

to be intrinsically unstable, unless nourished by a never-ceasing flow of energy and substrates for the synthesis of protein. Interruption of the dynamic state allows irreversible denaturation of a critical system, probably nucleoprotein in nature. The denaturation of protein, in general, follows a course such that the decay of any particular molecule is unpredictable, but the *probability* that each molecule will decay in a given period can be stated. The manifest result of such a denaturation process is the logarithmic death curve, the *logarithm* of the number of surviving organisms being proportional to time.

Whether "death" produced by an antibacterial agent is reversible or permanent may be determined, at least in part, by the firmness with which the drug is bound by vital cell constituents. The classic experiments of Gegenbauer[139] showed that the loss of viability induced by mercuric chloride in cultures of *Staphylococcus aureus* was reversible by simple washing for a certain time, after which the cells could still be revived by hydrosulfide. After a critical period neither method sufficed. Reversibility by either method depended upon *both* the drug concentration and the duration of contact.

Some compounds of the antiseptic-disinfectant group (detergents, tyrocidine and chlorine) kill through an obvious lytic action on the cell wall. Others kill more subtly, at a rate suggesting direct inactivation of a single nucleoprotein molecule per cell (Rahn[140]). These show a progressive increase in killing rate as concentration is raised, comparable to that seen in the effect of irradiation upon the reproductive mechanism. The same compounds at lower concentration stop growth and reproduction, but viability is not appreciably lost if organisms are soon enough removed from the antiseptic agent. Effects of this type are often associated with inhibition of respiration, both in growing cells and in resting cells supplied with substrate for combustion.[141, 142] In many compounds, therefore, antiseptic action seems to result from primary interference with energy-yielding catabolic reactions. All the effects of the antiseptic-disinfectant compounds are exerted upon nongrowing as well as growing cells.

The view that the chemotherapeutics under discussion — sulfonamides, penicillin and streptomycin — act upon the anabolic, protein-synthetic phases of metabolism is supported by two fundamental properties shared by these drugs: they exert their characteristic actions only (or most strikingly) upon growing cells; and they do not inhibit the respiration of resting organisms or the combustion of added substrates in the absence of growth. The loss of respiratory activity in growing cultures involves only the *extra* respiration associated with growth. In both respects these chemotherapeutics differ sharply from the antiseptic-disinfectant group.

Their intimate connection with growth and protein synthesis is further suggested by what is known of their mechanisms of action. The sulfonamides interfere with utilization of PABA in the synthesis of PGA, methionine, certain purine bases and perhaps other essential substances. Recent work with Neurospora mutants bears out the view that PABA may be a precursor of methionine.[143] Yet the evidence indicates that PGA is probably not an intermediate in the formation of these various compounds.[33] It is possible that PABA is a common precursor in a series of parallel reactions leading to different substrates for protein synthesis. If the purine bases thus formed are incorporated into nucleoprotein one would expect species-specific nucleic acids to antagonize the sulfonamides noncompetitively. This has not yet been investigated. Gale's finding that under conditions of growth sulfathiazole prevented the condensation of glutamic acid into peptide is exactly what one would expect if PGA or other glutamyl-PABA compounds were essential substrates in the process of protein synthesis.

Recent advances in nucleoprotein research have led to the conclusion that ribonucleic acid (RNA) occupies a central role in protein synthesis. It has been suggested that "nucleic acids serve as the agents which funnel energy into the protein synthesizing mechanism."[144] Rapid growth is associated with a high turnover of RNA.[145, 146] It seems significant that penicillin, at bacteriostatic concentration, inhibits ribonuclease, mononucleotidase and phosphatase, which together are involved in the depolymerization and dephosphorylation of RNA.[147-150] Furthermore, RNA is, to date, the only substrate, whose oxidation by nongrowing cells is inhibited by penicillin.[77]

RNA is again involved in the specific uptake of glutamic acid by gram-positive organisms, this assimilation being inhibited by penicillin during growth. The unusual sensitivity of the gram-positive group to penicillin could be attributed to a high affinity of the drug for this cell-wall RNA system, the combination leading to a glutamic acid deficiency for growth. Gram-negative organisms, although less sensitive, are nevertheless acted upon by penicillin. It must therefore be assumed that the drug disrupts RNA turnover within both types of cell.

The observations of Pratt and Dufrenoy on the –SH to S–S shift induced by penicillin, and those of Cavallito and his co-workers on the specificity of combination of penicillin with sulfhydryl compounds, have not yet been integrated into the picture. Ribonuclease, if it is a sulfhydryl enzyme, or its substrate, RNA, may require reduced sulfhydryl groups, or may be otherwise sensitive to an increased oxidation-reduction potential. It has, in fact, been

demonstrated that the integrity of the cell-wall RNA of gram-positive forms is especially dependent upon reduced —SH groups.[97, 98] Furthermore, staphylococci becoming resistant to penicillin and growing in its presence undergo two noteworthy changes: they adapt themselves to the higher oxidation-reduction potential by employing a wholly aerobic respiratory system[104]; at the same time they become gram-negative, and acquire the ability to synthesize the amino-acids whose assimilation was formerly mediated by the cell-wall RNA.[98, 101-103]

Evidence bearing upon the detailed mechanism of streptomycin action is still scanty. Sulfhydryl systems and RNA are both implicated by the few facts already established. Evidence that the drug can combine in a specific way with sulfhydryl compounds has already been reviewed. Streptomycin is reported to form a reversible complex with RNA, in competition with hydrogen ion and other cations.[118] The investigators suggest that although no enzyme is inhibited, RNA turnover is nevertheless disrupted, since access of enzyme to substrate is prevented. The preferential affinity of streptomycin for gram-negative forms is not clarified but may be connected with the lipopolysaccharide character of the cell wall in these species and the mycobacteria.

Obviously the facts at hand do not yet permit unification of all the clues into a single satisfactory theory. It is becoming increasingly evident, however, that antibacterial agents that have proved useful by virtue of a high chemotherapeutic ratio (in contrast to the antiseptic-disinfectant group) owe this property to a very specific interference with metabolic steps that are not shared to any important degree by host tissues. Comparative biochemistry has revealed how startlingly similar are many of the catabolic pathways and the mechanisms for elemental syntheses in all species from microorganism to man.[151, 152] Clearly, unique modes of protein synthesis and reduplication must underlie morphologic specificity. It is not surprising, then, that drugs that are to distinguish bacterium from bacterium and parasite from host should prove to interfere in a specific fashion with the pathway of protein synthesis.

(To be continued)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 35031

PRESENTATION OF CASE

A forty-seven-year-old unmarried woman was admitted to the hospital because of "inability to keep food down."

The patient stated that approximately one year before entry she had begun to have occasional vomiting after meals. This was attributed to nervousness. The vomiting became progressively more frequent, and eight months prior to admission it occurred once a day. She was always able to get liquid and soft foods down but could not swallow meat or other solids. When she attempted to eat solid food it "stuck" at the level of the lower end of the sternum, and in a few minutes the material was regurgitated, unchanged in appearance. There was no nausea or hematemesis. When she was successful in swallowing a piece of solid food she experienced pain in the region of the lower sternum and even more severe pain in the back at the lower thoracic level. The pain was dull in character and lasted about two hours. Milk of magnesia sometimes eased the distress. During the following months, until the time of admission, she was forced to restrict the diet to eggnogs, fruit juices and beef broth. She had lost 30 pounds in weight but had regained 8 pounds during the month before admission. There was considerable malaise. There was no melena, diarrhea or constipation. A roentgenogram in another hospital showed a stricture at the lower third of the esophagus, and she was subsequently referred to this hospital.

Four years before entry the patient cut her fingers on a glass. This was followed by intermittent attacks of coldness in the fingers, and the wounds became ulcerated and then gangrenous. A nerve block on the left side by injections for two weeks was carried out, but this did not help so a bilateral cervical sympathectomy was done. After a few weeks it was considered necessary to amputate the fingers and thumb of the left hand as well as the index finger of the right hand. Later the patient's feet began to remain cold all the time, and subsequent to this a bilateral lumbar sympathectomy was performed. She had no apparent progression of the disease since that time. She had been very

nervous following the operations and had not worked since that time. She lived with a nephew for a year, but at the end of this time he was married and the task of moving upset the patient considerably.

Physical examination revealed a thin, well developed woman in no distress. There was a Grade I blowing systolic, murmur heard along the sternal border. The aortic second sound was greater than the pulmonic. The lungs and abdomen were normal. The fingers and thumb of the left hand and the index finger of the right hand were missing. The skin of the remaining fingers was thick.

The temperature, pulse and respirations were normal. The blood pressure was 120 systolic, 60 diastolic.

Examination of the blood disclosed a white-cell count of 10,200. The hemoglobin was 15.3 gm. The urine sediment contained 1 or 2 white cells per high-power field. The blood nonprotein nitrogen was 17.0 mg., and the total protein 5.6 gm. per 100 cc. The prothrombin time was 15 seconds (normal, 16 seconds).

An electrocardiogram showed slight left-axis deviation.

A roentgenogram disclosed an annular defect of the distal esophagus about 5 cm. above the diaphragmatic opening (Fig. 1). The actual defect measured 1 cm. in length, with rather marked shelving above. Most of the compression appeared to be on the right and posterior side of the esophagus.

On the fourth hospital day an operation was performed.

Differential Diagnosis

Dr. Myles P. Baker: I think it might be instructive in discussing this case to put ourselves in the position of the ward officer confronted with this history and physical examination and discuss the diagnostic possibilities with just this verbal report of the x-ray examination in mind and then view the films later. Doubtless the nature of the deformity disclosed by x-ray study is going to be important diagnostically.

We are dealing with a middle-aged woman who developed dysphagia, regurgitation without nausea and substernal pain after swallowing solids for a year, coming on three years after symptoms, either of Raynaud's disease involving the hands and feet or scleroderma with Raynaud's phenomenon, the so-called acroscleroderma, had appeared. The diagnostic possibilities seem to me, first, that she had carcinoma of the esophagus, causing the filling defect in the lower third of the esophagus. It must be considered regardless of any other associated abnormalities found on physical examination. The symptoms that the woman complained of are in keeping with that diagnosis — namely, early minor dysphagia; substernal pain, reported as present in 75 per cent of cases of carcinoma of the esophagus and frequently radiating to the back; and regurgitation of food, mentioned by Vinson[1] as not being particularly common with cancer, and by others as being present in some 20 to 65 per cent of cases. Weight loss, marked in this case, is characteristic of the disease. The weight loss in this case was not progressive. The absence of anemia or marked hypoproteinemia might be looked on as a favorable sign indicating that one was not dealing with carcinoma of the esophagus. There must be cases of carcinoma, however, that present no anemia in which the patients look surprisingly well nourished.

Another possibility is benign stricture of the esophagus. The position of the obstruction here is 5 cm. above the diaphragmatic opening and is probably compatible with benign stricture of the esophagus and certainly much more so than with the entity cardiospasm, which is due to obstruction in the interdiaphragmatic segment of the esophagus — lower down than we have any evidence of in this case.

What basis have we in the history for any cause of benign stricture of the esophagus? There is no mention of chemical trauma, no antecedent acute infection and, indeed, nothing of history compatible with recurrent peptic esophageal ulcer; nor have we an x-ray report of the presence of diaphragmatic hernia or short esophagus, which are recorded as being so frequently associated with demonstrable peptic ulcer of the esophagus. We have no comment about the presence of a duodenal deformity such as a man might have who had had an active duodenal ulcer in the past — a finding frequently observed in patients with peptic ulcer of the esophagus.

We do have, however, this unique and, in the protocol, emphasized association of esophageal stricture with a past history of serious disease affecting the hands and feet, the precise diagnosis of which is a little difficult to be certain about on the data presented here. It is well known that real disturbance in esophageal function may be an early symptom in scleroderma, a disease that is certainly a rarity to me and, with esophageal symptoms, a combination that I personally have never seen. I found a reference to this association of esophageal troubles and scleroderma in an article by Lindsay, Templeton and Rothman.[2] They report 5 cases with varying degrees of esophageal stenosis in 3. Their first patient had initial symptoms of dysphagia due to benign esophageal stricture for one and a half years before developments similar to Raynaud's disease made their appearance. The third patient developed substernal pain one hour after eating food, with some relief on taking alkalies — as our patient had — followed about six months later by numbness and coldness of the fingers, with benign stricture of the upper border of the phrenic ampulla, as did their second patient, with scleroderma of two and a half years' standing,

and only minor dysphagia. The localized narrowing in these cases is about 4 or 5 cm. above the diaphragm and constitutes an abrupt change. Esophagoscopy revealed smooth scar tissue consistent with some ulceration about the stricture. The lumen of the stricture in one case was extremely small; there was also diffuse esophagitis from the middle third of the esophagus down to the area of the constriction or to a point about 4 or 5 cm. above the stomach. There was absence of normal peristalsis in the lower two thirds of the esophagus, accounting, they thought, for the impeding of swallowing fluid. The burning substernal pain they accounted for by the regurgitation of acid gastric contents through a relatively atonic cardia. They emphasized the fact that these constrictions occur at a point 5 cm. above the diaphragmatic opening as a result of previous ulcerative esophagitis at that area, the latter developing because of interference with normal esophageal peristalsis as a result of sclerodermatous changes. This must, of course, be a rare cause of esophageal obstruction, but the association here with the changes that this woman had in her hands and feet makes it an interesting possibility for speculation.

Did this patient have scleroderma? It is hard for me to determine, — perhaps it would still be hard had I seen the patient, — but the impression I get is that in true Raynaud's disease the sclerodermatous changes appear late in the disease, if at all. The troubles that this woman had with ulcerative, gangrenous changes in the fingers certainly came on rather quickly. It is true that vascular manifestations may be the ones that bring the sclerodermatous patient to the physician. In one series of 40 cases about 25 per cent complained early of coldness and intermittent vasospasm,[3] these phenomena becoming more and more prominent and occurring as in our patient with higher temperatures and possibly preceding skin changes by some time.

With these possibilities in mind let us ask Dr. Wyman to show the films to see if the constriction bears any relation to these few cases of obstruction recorded with scleroderma.

Dr. F. Dennette Adams: Is it not usually a progressive disease? Would you not expect it to be?

Dr. Baker: I suppose it is; but there must be a few cases — and I shall ask Dr. Lerman to comment later — in which it is largely restricted to the hands and feet, and less obviously to the face and chest, in which there is no pronounced progress.

Dr. Edward B. Benedict: I might say that the esophagus is involved in scleroderma in only a small percentage of cases. I have seen several cases, most of which showed severe esophagitis with some stricture and hemorrhage and erosion.

Dr. Stanley M. Wyman: The first two films are from an examination done elsewhere. They show the area of narrowing in the esophagus described in the protocol. There is a suggestion of an overhanging margin on the right lateral border of the esophagus above the narrowing. We have insufficient filling of the stomach or duodenum on this film to comment on Dr. Baker's question about the association of duodenal ulcer. I think it should have been looked for. There is, I believe, a definite, small, hiatus hernia. Examination done at the Eye and Ear Infirmary again shows the same diffuse narrowing with a suggestion of a small collection of barium on the right posterior aspect of the narrowed esophagus. The examination done here

Figure 1.

shows the same constriction and a small accumulation of barium suggesting a crater at the midpoint of this narrowing, perhaps 2 cm. distal to the beginning of the narrowing. Unfortunately these films are all taken in the same projection, but I cannot identify a true shelf formation, which I associate with carcinoma, and I believe that this apparent bulging of the esophagus proximal to the narrowing might be merely dilatation above the narrowing.

Dr. Baker: I should think this was a case in which esophagoscopy was indicated. I suppose that was done.

Dr. Lamar Soutter: It was done in the Eye and Ear Infirmary.

Dr. Baker: Findings at esophagoscopy would very definitely affect the decision to operate, I suppose, with resection or bouginage in mind. When I say "esophagoscopy," I mean esophagoscopy with

biopsy properly taken from the area of constriction. Both the history and the x-ray examination, as Dr. Benedict has pointed out, are inconclusive in obstructive lesions of the esophagus, and only by direct observation and by study of biopsy material can one be sure of what one is dealing with and of a proper decision about procedure.

As far as the diagnosis is concerned, in this particular case I would favor that of benign stricture rather than that of carcinoma of the esophagus. Whether it has any relation to the associated peripheral vascular disease or true acrosclerodermа is worthy of mention.

Dr. Donald S. King: Where does the so-called string sign come into a lesion like this, Dr. Wyman?

Dr. Wyman: I think the lesion is too high for it.

Dr. Jacob Lerman: Patients with Raynaud's scleroderma syndrome certainly show many bizarre manifestations. The course is variable. Sometimes the sclerodermatous lesions dominate, and sometimes the Raynaud symptoms. In answer to Dr. Adams's question we have seen patients who have progressed so far and then remain stationary for years.

Another point worth bringing out is that the sclerotic process that is present in the extremities is a universal process, and similar changes are seen in the myocardium and other organs. Some of these patients develop malnutrition as a result of the constant vomiting and with it an esophagitis on top of the esophageal fibrotic process, so that the picture on x-ray examination will be altered from time to time. The x-ray film shown is consistent with benign stricture complicated by esophagitis.

Dr. Benedict: I do not know the diagnosis or treatment in this case, but I assume that the operation performed was esophagoscopy with biopsy, since that is the only sure way to differentiate benign stricture from carcinoma. The importance of taking a biopsy cannot be overemphasized because the treatment of benign stricture is bouginage, whereas the treatment of carcinoma is resection.

Dr. Soutter: This woman was just as much a problem for us as she was for Dr. Baker today. On the ward we did not believe she had clinical evidence of scleroderma. We discussed that diagnostic point and concluded that she did not have scleroderma of the esophagus. The report from the esophagoscopist and the roentgenologist was that carcinoma could not be ruled out. The esophagoscopist did not see anything more than the upper limit of the lesion. He was not able to obtain an adequate biopsy. We thought that we would have to explore this woman's esophagus because of the possibility of carcinoma. Furthermore, in many people who have benign strictures there is more dilatation of the esophagus above the stricture than there is in these films.

In the operating room we found the esophagus thickened over a small area at about 8 cm. above the cardia. It was a dense type of thickening, and we could not decide on palpation whether it was some benign lesion in the wall of the esophagus extending through the muscularis or whether it was a carcinoma. A few years ago in a patient who presented a problem of this nature we opened the esophagus with a longitudinal incision, thinking we were probably dealing with a benign lesion but found a malignant one. Although that tumor was resected, we had recurrence in the chest cavity, which we thought was due to spreading the disease by cutting into the tumor. Therefore, in this case we believed that opening the esophagus in the presence of carcinoma might lead to metastases. So we could see no alternative but to resect the lesion.

Dr. Benedict: Dr. Soutter seems to be arguing that the fact that this esophagus was not dilated is in favor of carcinoma. I do not agree. It is true that in long-standing achylasia (cardiospasm) the esophagus becomes dilated, but not in benign stricture.

Clinical Diagnosis

Carcinoma of lower esophagus.

Dr. Baker's Diagnosis

Benign stricture of esophagus, unknown etiology.

Anatomical Diagnosis

Peptic ulcer of esophagus, with stricture formation.

Pathological Discussion

Dr. Tracy B. Mallory: The resected specimen showed a benign ulceration of the esophagus that had the characteristic histology of peptic ulcer. As is customary in such cases we found several islands of gastric mucosa in the esophagus. The wall of the esophagus beneath the area of ulceration was scarred and thickened, but we thought that that could be entirely explained as a secondary reaction to the ulceration of the mucosa and did not indicate a preceding sclerosis of the sclerodermatous type.

Following operation the patient developed progressive difficulties, the anastomosis failed to heal, and empyema developed. She died about one week postoperatively. At autopsy the remainder of the esophagus was free from any sclerotic changes. Sections from one of the nongangrenous fingertips showed endarteritic changes, nonspecific in character, such as are frequently seen in Raynaud's disease. There was nothing on which we could make a histologic diagnosis of scleroderma.

The only other finding of some histologic interest was marked cystic dilatation of the pancreatic glands, a lesion that I saw with some frequency in the Army and have seen very rarely in civilian life. In this case I have no explanation for it. I have seen it in people very severely ill for a week or more before they die, frequently in cases of infectious

disease but also associated with various other conditions such as uremia.

DR. WYMAN: Did this woman have a duodenal ulcer?

DR. MALLORY: None was found.

DR. BAKER: This was more than esophageal ulcer and spasm — definite stricture?

DR. MALLORY: Definite ulceration with marked scarring and narrowing of the lumen.

DR. KING: Is it your impression that most of them are lower than this?

DR. MALLORY: Yes; this was relatively high.

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CASE 35032

PRESENTATION OF CASE

A thirty-nine-year-old woman was admitted to the hospital because of easy fatigability, pain in the left anterior chest and the presence of an abdominal mass.

One year before admission the patient first noted a sharp pain in the left anterior chest. The pain radiated across the left anterior chest to the axillary line, up into the axilla and down the inner aspect of the left arm to the wrist. At times the fingers became numb in association with this pain. About a year before admission she developed sharp, crampy, pelvic pain. There was no associated vomiting or bowel irregularity. The menstrual periods became irregular, and the amount of flow decreased. A hysterectomy for fibroids was done nine months before admission, with relief of the pelvic pain. No pelvic masses, except for the fibroids, were seen at operation. An appendectomy and right oophorectomy had been done nine years before admission.

Physical examination revealed a left-lower-quadrant mass. The cul-de-sac was empty, and the mass, approximately 6 cm. in diameter, rode up out of the pelvis. The heart was not enlarged, and the apical rate was regular.

The blood pressure was 160 systolic, 95 diastolic.

Examination of the urine and blood was within normal limits. A Graham test was negative. A barium enema was reported as showing no evidence of intrinsic involvement of the colon, but the colon was displaced by an extrinsic mass (Fig. 1).

On the fifth hospital day a laparotomy was performed.

DIFFERENTIAL DIAGNOSIS

DR. GORDON A. DONALDSON: I doubt very much whether the first perusal of this history has left any of you colder than it did me. On looking at it further, however, it is possible to summarize some of the salient points and find that approximately a third of the history can be accepted as a definite fact — namely, that the patient had a hysterectomy and that the right tube and ovary had been removed earlier. My only comment about this portion of the history is that we would like to know why the right ovary was removed nine years earlier. What was

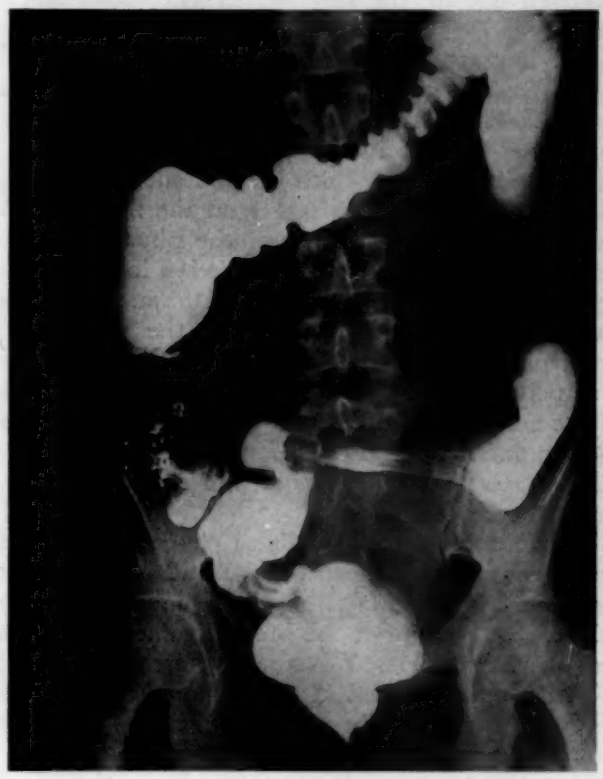

FIGURE 1.

the lesion? I am a little suspicious of a fibroid causing sharp, crampy, pelvic pain and wonder if something was overlooked in the pelvis nine months before at the time of laparotomy. Also, I would call attention to the cautious statement "no pelvic masses, except for the fibroids" were noted at this time. I wonder how much search was made for the left ovary.

So we are left with a thirty-nine-year-old woman with pain in the upper part of the torso and a mass in the lower part of the torso, both on the left side. It is always dangerous to make two diagnoses at these conferences, but unless the x-ray film can help us considerably I think we may be forced to.

DR. F. DENNETTE ADAMS: May I interrupt at this point to answer some of these questions. When the appendix was taken out the ovary was said to have a cyst in it and was also removed. Both operations were done in another city. The story I obtained on the second operation was that the uterus was deformed, not by fibroid tumors, but by some congenital abnormality. The left ovary was said to have been removed with the uterus. Both operations were done by a capable surgeon in another city.

DR. DONALDSON: Can we accept that as a fact?

DR. ADAMS: All I can say is that the surgeon who did the operation is highly capable and that the uterus and the left ovary were reported to me, although not by the surgeon, to have been taken out.

DR. DONALDSON: May we see the x-ray films?

DR. STANLEY M. WYMAN: The gall bladder is normal. The plain film of the abdomen shows a soft-tissue fullness in the pelvis, slightly more to the left, and rising up into the abdomen, overlying the sacrum. It appears larger on the film than it seems from the description of the physical examination. One cannot be sure if this is a lobular mass or includes two or more separate masses. The barium-enema examination shows the sigmoid to be displaced upward, apparently by a mass in the true pelvis, with a second mass or possibly a lobule of the mass rising above it at this point. The bones appear normal as far as I can see on these films. The masses are homogeneous and show no calcification.

DR. DONALDSON: This is a huge mass that developed in nine months, and I still believe, from its position in the x-ray film, that it must have been related to the base of the broad ligament, perhaps the ovarian pedicle. Was the hysterectomy total?

DR. ADAMS: I think it was. I could not feel the cervix when I did a pelvic examination — for what that may be worth.

DR. DONALDSON: We can eliminate the colon because of the lack of history and the negative barium enema. Prolapse of an organ high in the abdomen such as the stomach or kidney or omental tumor is very unlikely. I still believe that our information concerning the left ovary is not completely black and white, and we should still consider the possibility of disease in the left ovary or remnant of the left ovary. As a matter of fact, I am really thrown off guard by the added information that the left ovary was absent. I had a good story worked out for it. One was a fibroma, the Meigs syndrome, an unlikely possibility, however, because of the site of the chest pain. The tumor was described as 6 cm. long, which is just about right for a fibroma. This tumor is much larger than that, and the possibility of carcinoma with metastasis to the lungs came to mind, but the patient seemed to be in too good shape to have had a metastatic lesion in the lung for a full year. I suppose we ought to consider a residual, simple cyst of the left ovary.

Finally, an endometrioma with pulmonary metastases is something that has been reported. I glanced through the literature and found that there have been pulmonary metastases from endometriomas of the ovary. This picture is consistent with that, but perhaps, again, the size of the tumor throws out that diagnosis. An endometrioma 6 cm. in diameter could have developed over the course of a year in a thirty-nine-year-old woman, and it is probable that she could have had symptoms from a properly placed metastasis in the left lung.

DR. ADAMS: May I interrupt again because I believe that the history is not fair to Dr. Donaldson. This pain in the chest had existed, to my knowledge, for two and a half years. The patient described what sounded like anginal pain, but I do not believe she actually had angina. The pain in the chest existed long before any of the pelvic symptoms appeared.

DR. DONALDSON: I wondered if it was cardiac pain. She was slightly hypertensive, perhaps menopausal.

DR. ADAMS: That was the only observation of high blood pressure. I always found her pressure normal in my office.

DR. DONALDSON: Because of the lack of any history of angina and the presence of numbness in the fingers it is an unlikely possibility.

The possibility of a cervical rib or tight anterior scalene muscle as a cause of such pain might be considered. It is unusual for such a syndrome to produce pain in the anterior chest wall itself. We ought to consider perhaps a slowly growing lesion of the chest wall or of the lung, such as a Pancoast tumor with metastases to the pelvic organs. Again, the patient was too young and apparently too well, and the history too long. I think it would be unusual for this woman to have such a lesion. I believed that endometrioma with metastases to the lung was the best bet. Against this is the fact that the tumor was so large, but I suspect that an endometrioma could have developed to this size in nine months' time.

DR. JOHN MCL. MORRIS: Is there a chest film?

DR. ADAMS: It was normal. How recently it was done, I do not know.

DR. TRACY B. MALLORY: Are there any other suggestions?

DR. GRANTLEY W. TAYLOR: A mass 6 cm. in diameter riding out of the pelvis would not push the transverse colon up. I wonder if Dr. Adams has a note on that.

DR. ADAMS: I felt it, so it must have been pretty big.

A PHYSICIAN: Was she given estrogen for the menopause?

DR. ADAMS: Some time ago she was given an estrogen preparation for a while. It was stopped before hysterectomy. After that she received none. The note I made before she came to the hospital was that she had a mass up to the umbilicus.

DR. MALLORY: The question that I would have liked to ask at this point is whether the sponge count was certainly correct at the last operation.

DR. ADAMS: I did not ask that one.

DR. WYLAND F. LEADBETTER: Is the x-ray compatible with an anterior meningocele?

DR. WYMAN: There is no evidence of anything definite in the spine. It is a little unlikely to have anterior meningocele so low to the left of the midline, and it looks like two masses or a lobulated mass.

DR. JOE V. MEIGS: I have now seen three anterior meningoceles — two retroperitoneal at the midline, and the third on the left side. One could feel them fairly well.

DR. MALLORY: Are there any suggestions from the x-ray point of view?

DR. WYMAN: This is a homogeneous soft-tissue density that may be lobulated or may be multiple.

DR. DONALDSON: It is very unlikely for a lymphoma to present such a picture. I will stick to my diagnosis of endometrioma.

CLINICAL DIAGNOSIS

Ovarian cyst.

DR. DONALDSON'S DIAGNOSIS

Endometrioma.

ANATOMICAL DIAGNOSIS

Hematoma of broad ligament and sigmoid mesentery.

PATHOLOGICAL DISCUSSION

DR. MALLORY: Dr. Parsons, will you take up the story?

DR. LANGDON PARSONS: The chest pain is obviously a red herring, and I did not have to consider that because Dr. Adams told me to let that alone. This mass was not in the pelvis, but rode up above it to the level of the umbilicus. Aside from the history the strongest point against ovarian cyst was that at pelvic examination the mass did not descend at any point into the pelvis. At operation we were confronted with a voluminous, blue-domed cyst lying between the broad ligament and the leaves of the sigmoid. At first I thought it was an ovarian cyst, but I soon found that I could not get around it and that it was retroperitoneal. It was actually pretty much on a level with the pole of the kidney, and the majority of it lay within the leaves of the sigmoid mesentery. I found a normal left ovary. As far as I can reconstruct this thing I believe that at the last operation the stump of the retained ovary was buried between the leaves of the broad ligament. Hemorrhage followed, and the hematoma gradually spread from the broad ligament into the sigmoid mesentery. We evacuated the hematoma, which drained about two liters of bloody fluid, and took a few biopsy specimens from the wall of the cavity.

DR. MALLORY: Our fragments from the wall showed only granulation tissue, organizing blood clot and hemosiderin, all evidences of old hemorrhage. We looked for endometriosis and found no evidence of it.

DR. PARSONS: We have talked about the rarity of cysts of the retained ovary. I do not think that we see many.

DR. ADAMS: Did you say that you found the left ovary?

DR. PARSONS: A normal left ovary.

DR. MEIGS: We do not see many cysts in retained ovaries — in fact, extraordinarily few. We have only seen one or two in the Vincent Memorial, although we leave an ovary in whenever possible in women who have not reached the menopause.

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FISH OR CUT BAIT

THE medical profession, which has made such impressive advances along clinical and scientific lines, must decide, and shortly, whether it has also the ability and the interest to maintain and control and modernize its own time-honored standards of service.

To do this it must sacrifice certain of its cherished beliefs of other days. It must to some extent submerge, for the sake of a wider distribution of its benefits, that personal independence and freedom of action so characteristic of the private practitioner of medicine. It must freely acknowledge that any form of voluntary health insurance that offers a decent standard of medical care to all economic and social groups is more effective than the individually bestowed charity for which it has been so conspicuous, and that has always been so freely given.

It must realize that it is functioning in a world in social revolution, and that slow evolutionary processes of change are not adequate to bring it up to the times and keep it abreast of them. It must understand that the only apparent alternative to such a remodeling of its methods is capture and eventual domination by other forces that, lofty as their motives may be, have yet but a limited understanding of the traditions, the ideals and the technics that they seek to control.

The profession of medicine must, and must now, come fully awake to its responsibilities, to the dangers that threaten it — and to its own strength. It must make up in a few brief months for years lost in the cultivation of its public relations. It must teach a forgetful public what that public owes it; it must acknowledge openly what it owes the public, and present its plan of payment. It must acknowledge its inertia, its blunders and its former indifference to public opinion, and wash them out.

It must show its receptiveness to new ideas and its ability to discuss their common problems with all agencies that are honestly seeking the same goal of service.

To do these things now and effectively requires money — not a war chest or a slush fund, as it has been termed by the chief protagonist of compulsory insurance, who has the resources of a federal agency with which to promulgate his own ideas — but an educational fund to put clearly before the public the accomplishments and the capacities and the honest intentions of a free but united profession.

The proposed assessment is necessary in order that the American Medical Association, *representing the medical profession of the country*, may put its relations with the public on a sound basis. If the assessment is paid with some scolding and a lecture, then let it in that way be given, for criticism may serve two purposes — to relieve the critic and, so far as it is constructive, to guide the recipient. The important thing is for every member of the profession now to rally to the support of his ancient and honorable calling, to show his pride in it and to contribute to the maintenance of its standards and its prestige. The secretary of the Massachusetts Medical Society, acting in this instance only as an agent of the American Medical Association, is taking the steps necessary to collect the assessment for the parent organization. The physicians of Massachusetts are urged

to do their share, and promptly, in implementing the program that is being planned.

There is today one vital consideration for physicians to remember. They must work in harmony if they are to achieve through their own initiative those things that others believe can be achieved better by methods of compulsion.

HEMODYNAMICS IN THE LUNGS

Until comparatively recently, knowledge of abnormal changes in the blood pressure in the pulmonary circuit has been largely speculative. It is now possible to make direct measurements of the blood pressure in the arterial portion of the pulmonary circuit and to relate abnormalities in such pressures to clinical and post-mortem findings. The full implications of such studies, now being carried out in a number of laboratories, are likely to be profound.

Pulmonary hypertension has been recognized as a rather indefinite clinical entity for many years. Pulmonary vascular sclerosis has been familiar to pathologists since the middle of the last century. One of the most illuminating, if somewhat neglected, monographs on the latter topic is that by Ljungdahl,[1] which appeared in 1915. In this work, sclerotic changes in the pulmonary vessels were shown to be relatively frequent in mitral stenosis and to occur in certain congenital cardiac lesions, notably patent ductus arteriosus, in some cases of pulmonary emphysema and in the obscure and rare entity known as primary pulmonary vascular sclerosis. It is also likely that such vascular disease occurs in some cases of cardiac decompensation on a hypertensive or arteriosclerotic basis.

With the modern technics now available it is possible to study in the living patient the alterations in pulmonary arterial blood pressure that have, largely by implication, been said to accompany pulmonary vascular sclerosis. Of much greater importance is the likelihood that, by establishing the presence of pulmonary arterial hypertension, the investigator can predict the presence of vascular changes within the lung. Such information not only may prove to be of great prognostic value but also may be of considerable value to the surgeon when the proposed operations for mitral stenosis become a practical matter.[2] The surgeon may logically expect to obtain his best results in patients who have not developed pulmonary vascular sclerosis and therefore to urge operation relatively soon after the valvular lesion is discovered. Similarly, in cases of patent ductus arteriosus, complete relief from symptoms after ligation should probably not be predicted if the pulmonary arterial pressures and clinical symptoms indicate that advanced pulmonary vascular sclerosis is present.

The new technic has already thrown considerable light on some of the many perplexing questions having to do with cardiac failure and the pathogenesis of such related phenomena as pulmonary edema and paroxysmal nocturnal dyspnea. Before these events can be completely understood some means of measuring pressures in the left atrium and in the venous portion of the pulmonary circuit must be developed. Even without such means etiologic understanding and genuinely rational therapy are being furthered by those engaged in studying pulmonary arterial pressures.

The entire field is one of great promise and is still another example of the benefit that accrues to medical science when investigators avail themselves of sound existing knowledge and develop imaginative technics, whether morphologic or functional. It is also another example of a basic research endeavor that has, in a relatively short time, proved to possess great practical significance.

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CARE OF THE MENTALLY ILL

The twenty-ninth Annual Report of the Massachusetts Department of Mental Health was presented as required by law to the Governor and Council on November 3, 1948, by Dr. Clifton T. Perkins, commissioner of mental health of the Commonwealth.

A few extracts from this report, which points out the deplorable conditions that exist for the care and treatment of mentally ill patients in the Commonwealth, are pertinent.

One of the greatest problems in the field of mental health, according to Dr. Perkins, is the absence of any broadly based, mature application of an in-

formed public opinion to serve a state department as an intelligent, critical and effective supporter as the situation may from time to time demand. This statement of Dr. Perkins is particularly applicable to the members of the medical profession, probably few of whom are well informed about the conditions as they exist.

In general, the report continues, the Department is responsible for providing for the efficient, economical and humane management of the state hospitals and may establish by-laws and regulations for the government of those hospitals, of which there are sixteen, caring for approximately 30,000 patients. It is pertinent also to realize that 95 out of every 100 persons in the Commonwealth who need mental hospitalization must be cared for in the state hospitals because they cannot afford the price of private facilities. For better or worse, the State has a practical monopoly — the fate of the mentally sick citizen is literally in its hands.

The report furthermore shows clearly that the responsibilities mentioned are not being adequately met. The Commissioner points out that World War II materially reduced over-all medical standards in the state program because of the inability of the Commonwealth to compete in the manpower crisis, and the inexorable demands of the armed forces. Recovery has not yet been made from that reduction of standards.

Basically, there are "not enough well trained doctors or nurses or occupational therapists or other personnel indispensable to the proper bedside care of patients and execution of therapeutic programs either within the hospital or the clinics."

The quotas allowed for the work by the state are less than the standards deemed minimum by nation-wide agencies in the field of mental health, but even these quotas are not met. In the quota allowed for physicians there was as of September, 1948, a vacancy of 25.44 per cent; in the ward services the vacancies amounted to 30.88 per cent.

The loss of every trained doctor, according to the report, entails years of training for the physician who is to replace him.

> Mere swapping of holders of M.D. degrees does not make up for the loss. . . . The doctors we have lost almost without exception have gone where they can get more cash, have less restrictions in regulating their lives, where more adequate personnel is available in the ancillary fields to help them in their work.

> Doctors, like other scientific men, will take just so much pushing around financially and otherwise. Compared with the competition, the Commonwealth has failed to realize this fully.

The Commissioner in this statement puts his finger on the fact that to provide a satisfactory medical service the pay must be on a competitive basis, but there must be, in addition, a proper atmosphere in which a physician can flourish. He further points out that teaching and training activities constitute one of the best ways of maintaining an active and alert staff and emphasizes the importance of research as an outlet for an active staff.

Unless the conditions for the care and treatment of the *mentally ill* patients are promptly improved, there can only occur a demoralization that is bad for both the community and the medical men who make up a part of the community. It appears that the physicians of the Commonwealth, individually and through their medical societies, — state, district and local, — would be well advised to inform themselves of the conditions as they exist and take an active part in their improvement.

HISTORY OF PHARMACY

THE first Pan-American Congress of Pharmacy, meeting in Havana late in 1948, gave official recognition to the American Institute of the History of Pharmacy at the University of Wisconsin. The Institute was named "as the center of the endeavor in the history of pharmacy in America."

Through a more formal representation of Latin-American countries in the Institute, with a trustee in each of them, it is hoped that investigations into the history of pharmacy will be broadened and a series of monographs may be published on the history of pharmacy in all the countries of this hemisphere. Among the more practical aspects of the congress was the discussion concerning unification of official drug standards and the publication of a Pan-American pharmacopeia.

Practicing, during the development and progress of his ancient profession, similar forms of magic and mystery, the pharmacist finally emerged as a true scientist at about the same time as did his co-partner in the investigation of drugs, the physician. Modern medicine owes much to this continuing partnership.

CORRESPONDENCE

REGARDING THE AMA ASSESSMENT

To the Editor: You may have seen the recent press statement that those who control policy in the American Medical Association have voted to assess all members $25 each. And that the proceeds ($3,500,000) are to be "spent on a campaign of 'education' to tell people the advantages of the 'American system' of medical care." There is no evidence that this sum will be used in an unbiased search for facts or in the promotion of impartial discussion. On the contrary, judging by past editorials in the *Journal of the American Medical Association*, the actual purpose is to influence opinion in one direction by presenting one side of a controversial issue.

This is not education, it is propaganda. Should American doctors be subjected to such an extraordinary tax without their consent? Even if such action by the American Medical Association officials should be pronounced legal, I believe that it is unethical.

Therefore, I suggest that the *New England Journal of Medicine* and the Massachusetts Medical Society openly oppose any such tax until a referendum has been held.

It would be possible for a voting slip to be inserted in each copy of the *Journal of the American Medical Association* for one issue after January 1. Until some such referendum is held I have no intention of paying this tax.

HENRY S. FORBES, M.D.

Milton, Massachusetts

To the Editor: The many inquiries concerning the recent decision of the House of Delegates of the American Medical Association to assess each member $25.00 indicate a need for classification of many aspects of this charge. Very little information is provided by the editorial in the *Journal of the American Medical Association*, which announces the decision and states that the purpose is "to provide a fund adequate for meeting the proposal of the present administration and particularly the present Federal Security Administrator to nationalize the services of the medical profession through the enactment of a compulsory sickness insurance act covering every person in the United States."

Before paying the assessment many doctors want to know (indeed should know, if they are to act as intelligent physicians and citizens) a few simple things about the assessment. Is the money raised to be spent by the county medical societies, by the state medical societies or by the American Medical Association? Is it to be spent merely in *opposing* by reiterating, as Mr. Baruch says, "what not to do" or by *proposing* constructive action? If the constructive action pertains to voluntary insurance will endorsement of voluntary plans be limited to Blue Cross Hospitalization and Blue Shield Medical Service or will well organized plans such as The Health Insurance Plan of New York City, the Permanente Foundation Health Services of California and the Labor Health Institute of St. Louis be encouraged? Will opposition to General Hawley's proposals concerning Blue Cross and Blue Shield continue?

Many doctors, particularly the younger members, who may have little vested interest in current medical practice and but little professional or other income, want to know if this assessment is compulsory in the sense of losing membership or good standing in the county and state medical societies and hence the American Medical Association, or even of receiving prejudiced consideration as applicants to or members of hospital staffs.

That young physicians can fear such a possibility is not only a serious reflection upon the ethics of the profession but also a serious threat to the future of the American Medical Association. Up to now membership in a county and state medical society and the American Medical Association has frequently been used as a qualifying requirement for positions on many hospital staffs or other professional privileges. If membership becomes contingent upon paying an assessment that more than doubles the income of the American Medical Association and is to be used to oppose legislation endorsed by the President of the United States and the majority party of Congress, a major purpose of the American Medical Association becomes not only political but also highly controversial. Under such circumstances if political rather than professional considerations determine membership, can the American Medical Association continue some of its important roles? For example, can membership any longer carry a connotation of professional qualification that places nonmembers at a disadvantage?

Compared to jeopardizing such traditional functions the question of what will happen to the American Medical Association's tax status as an educational and nonpolitical organization is of minor concern. In this connection one wonders why the House of Delegates decided to have the American Medical Association raise this money itself rather than continue having it done by the National Physicians Committee, which already ranks as one of the top lobbying organizations in the country.

Many of these questions must have been debated by the House of Delegates in arriving at its decision to make the assessment. That the debate was held in executive session, therefore, seems unfortunate, for it is unlikely that members of the House would have said things that the public should not hear, and its answers to many questions should be enlightening. If the debate provides them, it would appear deserving of publication. If not, provision for tolerant discussion and considered debate seems essential to a democratic professional behavior, to an enlightened professional opinion and to a respect for that opinion by the public.

Ironically, should discussion be suppressed and physicians pay the assessment under compulsion, would not the American Medical Association be practicing what it professes to abhor — namely, domination by a federal or national body of state and county units that constitutionally are autonomous?

I trust that the Massachusetts Medical Society will deal with this matter according to its traditionally New England democratic way.

ALLAN M. BUTLER, M.D.

Massachusetts General Hospital
Boston

To the Editor: The people's mandate, handed down at the polls on November 2, 1948, is frequently interpreted as requiring federal participation in the provision of less expensive and more extensive medical care for the American people. Whatever physicians may have believed before November 2, the attitude of the public toward health legislation should be reasonably plain at present. Whether the entry of the federal Government into the field of medical care on a large scale is wise or foolish, the possibility of it is nearer than ever before. Blind opposition to this possibility is an invitation to disaster. Neither the medical profession nor any other professional or occupational group can successfully defy the majority rule in the United States as now constituted. For the profession to attempt such defiance would be tragic indeed; it would inevitably mean the lowering of organized medicine in the eyes of the public to the position of an economic pressure group, surely an ignominious decline from a position deserving and receiving the faith and trust of layman and physician alike.

The Government's plans to solve the nation's medical economic problems have been published for all to see. Mr. Oscar Ewing, the federal security administrator, and his advisers have produced a plan that they believe will meet our needs. The plan includes provision for compulsory health insurance, a feature that may well be neither desirable nor necessary at the present time. Be that as it may, no reasonable person can doubt that Mr. Ewing and his colleagues have made a serious effort to master an enormously complex socioeconomic problem and to provide effective remedies, acceptable to the nation as a whole. It is ridiculous to regard the plan as the instrument of Leninism, and it is naïve to believe that, even if made into law without a change, it would communize American medical practice. It is just as ridiculous to accept it as the perfect answer to the nation's needs or to assume that it must pass the Congress unchanged and unamended. Meek acquiescence on the part of the profession to the bill as it now stands is unthinkable.

If the profession must accept the near-reality of federal participation in the provision of medical care, what, then, should be its attitude toward the Ewing Plan? A specific, point-by-point answer is urgent, and for it to be effective it must concern itself primarily with *improved standards of medical care* and secondarily, if at all, with the status of the physician. The tremendous uproar over medical care in this country, and the objections of the medical profession to plans and planners, have centered too much on the prestige, the

dignity and the rights of the physician. Improvement of medical standards as a primary goal has been sadly obscured by both groups. The Ewing Plan is an economic plan designed to provide abundant, low-priced medical care to everyone, but not concerning itself specifically with improving the standards of medical practice. Similarly, the profession's objections to the plan have been based largely on the protection of free enterprise and the status quo, either by direct statement or by implication, although medical standards have occasionally been dragged in to underscore an economic point. The unfortunate tendency of some professional groups to concern themselves primarily with financial matters led one highly respected medical spokesman, H. J. Morgan, in an article entitled "Professio" (*Ann. Int. Med.* **32**:887-891, 1948) to say:

> One of our so-called professional organizations has emphasized economics and the material aspects of medical practice so vociferously and forcefully as to lead some of the people and some of the people's representatives in government to consider it a business or trade organization. A Federal Court decision revealed in no uncertain terms that Medicine in the United States, in this instance, forfeited its professional status before the law. It appears that by word and deed we interpreted ourselves to the people and the courts as tradesmen.

It is still not too late to do our own house cleaning. An effective plan embodying federal participation, must be evolved by the profession itself, and it must be one that will inspire the confidence instead of the distrust of the public. The plans offered by organized medicine to date have been defensive plans, designed to change the *status quo* as little as possible. An entirely new approach is essential. It must be based primarily on the intent to distribute high-grade medical care as widely as possible. There must be no reluctance to alter the *status quo* merely because of fear of change. The profession must set up its considered plan for the *ideal* system of medical care. No stop-gap compromise will suffice as a master plan. From its plan for the ideal system, the profession and other medical planners can then proceed to arrange the details, economic and otherwise, to suit the circumstances. An imaginative and courageous approach of this sort will stand in sharp contrast to the grumbling and lusterless schemes currently being brought forward by the profession to counter the popular, but usually defective, offerings of Government planners.

The perfect solution has not yet been presented. It is the medical profession itself that must evolve and present it. There should be no more jousting at windmills. The profession should brutally scrutinize its own conscience, examine the facts and set the pace, not only for the political planners but also for itself. By audacious and sober action, it can regain its position as the profession of integrity and unassailable standards. If its actions continue to be motivated merely by blind resistance to change it will reap catastrophe, the full extent of which no man can now foresee

CARLETON B. CHAPMAN, M.D.

Minneapolis, Minnesota

To the Editor: Certain recent inquiries and comments concerning the action of the American Medical Association in assessing its members twenty-five dollars are disturbing. Hypercritical comments from those committed to compulsory national health insurance have validity commensurate with their underlying logic. Adverse criticism based on lack of information is entirely another matter.

At the annual meeting of the American Medical Association in Chicago in June the House of Delegates voted to raise the levying level through dues or assessment to twenty-five dollars. The extensive activities of the parent organization have been heretofore conducted without dues or assessment other than the amount paid for subscription to the *Journal of the American Medical Association*. At the recent interim session conducted in St. Louis the full House of Delegates for reasons sufficient to our delegates unanimously voted the maximum assessment.

There may well be valid criticism of the existing structure of our medical house. Minority opinion may not be adequately represented. But certain basic facts are valid. The House of Delegates of the American Medical Association is composed of state-society members elected on a proportional basis. When we castigate the American Medical Association in public we are castigating ourselves. When the house is on fire is no time for a jurisdictional dispute over who should man the hose.

The St. Louis assessment because of its urgency could not apparently be discussed in advance of the meeting. The response to the assessment as voted has not been good in the press generally and has been universally poor among the more vocal proponents of federal planning.

Most of us need information on the basic facts at issue. An extensive educational campaign for physicians and for the public is immediately forthcoming. A few million dollars for the job to be done is inconsequential in view of its importance.

Final judgment on the assessment should be withheld until the reasons that produced a unanimous vote of the House of Delegates are made known to all of us. This information is on the way. In the meantime, one aspect of this issue is clear. Our delegates have acted. Our organization has acted. Are we with it?

JOHN F. CONLIN, M.D.

Boston

BOOK RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Diagnosis in Gynaecology: A classification of gynaecological diseases based on aetiology and the clinical logic for diagnosis. By James V. Ricci, M.D., clinical professor of gynecology and obstetrics, New York Medical College, director of gynecology of the City Hospital, New York, director of gynecology and obstetrics, Columbus Hospital, attending gynecologist and obstetrician, Flower and Fifth Avenue Hospitals, New York, and consultant in gynecology and obstetrics, Beekman-Downtown Hospital, New York. 8°, cloth, 259 pp. Philadelphia: The Blakiston Company, 1948. $4.50.

This manual is based on the clinical demonstrations given to students of the New York Medical College. A fundamental knowledge of gynecology is necessary for its profitable use. A new type of classification by genital structures and their diseases is used instead of the usual classification by diseases. The preliminary chapters are devoted to the general subjects of anatomy, female sex hormones, diagnosis and symptomatology and general classification. A good index concludes the volume. The book is well published.

NOTICES

ANNOUNCEMENT

Dr. Joseph A. Dubins announces the removal of his office to 314 Commonwealth Avenue, Physicians Hall, Boston.

NORFOLK DISTRICT MEDICAL SOCIETY

A meeting of the Norfolk District Medical Society will be held at the Boston Medical Library, 8 Fenway, Boston, on Tuesday, January 25, at 8 p.m. The following scientific program, entitled "Geriatrics," will be presented:

Problems of the Aging. Theodore G. Klumpp, M.D.
The Surgical Care of the Aged. John Homans, M.D.
Medical Aspects of Growing Old. Robert T. Monroe, M.D.

The meeting, which will be followed by a collation, is open to all physicians.

NORFOLK DISTRICT WOMEN'S AUXILIARY

A meeting of the Women's Auxiliary of the Norfolk District Medical Society will be held in the State Suite, Copley Plaza Hotel, Boston, on Tuesday, January 25, at 3 p.m. Miss Elizabeth Wilson, actuary, statistician and author, will speak on the subject "Socialized Medicine in England."

(*Notices concluded on page xiii*)